Evidence Report:

Risk of Early Onset Osteoporosis Due to Space Flight

Human Research Program

Human Health and Countermeasures Element

Approved for Public Release: May 9, 2017

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I. PRD RISK TITLE: RISK OF EARLY ONSET OSTEOPOROSIS

Risk Statement: Given that some parameters of skeletal adaptation may not be reversible after return to Earth, there is the possibility that early onset of osteoporosis may occur.

Description: Bone minerals decline in microgravity, and bone mineral density (BMD) losses of approximately -1 to -1.5% per month were calculated for astronauts serving on long-duration missions prior to 2009. It is unclear whether BMD losses will stabilize with time in space, or continue to diminish with time. In addition, it is unknown if fractional gravity, present on the moon and Mars, will mitigate the mineral loss. Clinicians diagnose osteoporosis in premenopausal females and males younger than 50 years on the basis of BMD T-scores $\leq$ -2.5 (hip and lumbar spine) accompanied by clinical evidence of a fragility fracture. If mission-related changes to the skeleton cannot be corrected by rehabilitation after the mission, crewmembers could be at risk for premature osteoporosis-related fractures in later life. To mitigate this risk it is necessary to understand the dynamics underlying the BMD changes that occur in microgravity, to monitor for the persistence of changes after space flight, and to evaluate if and how current and future osteoporosis treatments might be used to mitigate the risk of long-term skeletal problems in astronauts.

II. EXECUTIVE SUMMARY

After early space flights confirmed that humans could survive in the space environment, seminal investigations focused on how the skeleton adapts to microgravity, and how microgravity might influence the following skeleton functions: (1) as a reservoir to maintain mineral balance, (2) as a protective structural framework for internal organs, and (3) as a lever for muscle attachments to facilitate mobility. During some of the first experiments in astronauts, investigators evaluated calcium balance (intake vs. excretion) and tested new technologies in bone densitometry. The advent of dual-energy X-ray absorptiometry (DXA) resulted in an X-ray based technology to measure areal bone mineral density (aBMD) that has greater measurement reproducibility, shorter scan times, low radiation, and an ability to quantify multiple skeletal sites from a whole body scan. Multiple large prospective studies have used this clinically-useful technology to predict fragility fractures. Consequently, the World Health Organization (WHO) proposed that an aBMD T-score < -2.5 (referenced to average aBMD of young white females) be used as a guideline for diagnosing osteoporosis. Soon thereafter, NASA perceived that this evidence-based clinical test could be used to monitor skeletal health in active astronauts, to define the effects of space flight in astronauts, and to assess whether skeletal health is restored to baseline levels after return to Earth.

When the Human Research Program (HRP) was initiated in 2006 there was already an overarching concern that the aBMD-based T-score guidelines were not applicable to the astronauts. The guidelines were developed to identify postmenopausal females who require treatment with osteoporosis therapies. Specifically, the guidelines could be applied to perimenopausal and postmenopausal females and to males older than 50 years. There was no aBMD-based cut-off-point with which to identify "osteoporosis" in either female astronauts who were premenopausal or in male astronauts who were younger than 50 years. Thus, in 2010 a panel of experts was convened by NASA to review the accumulated clinical and research data

from astronauts who had flown on long-duration (> 30 days) missions (n=35). The panel consisted of experts in osteoporosis, endocrinology, rheumatology, gerontology, physical medicine, and rehabilitation, with subspecialties in bone densitometry, bone epidemiology, male osteoporosis, and nutrition. Panel members for this NASA Bone Summit were practicing clinicians with knowledge of bone loss in terrestrial populations and acted as either principal investigators or as consultants on research studies; some panel members served as policy-makers and position developers in the osteoporosis field. Panel members were asked to convey the "trigger" that would drive them to intervene clinically to mitigate a premature onset of osteoporosis in astronauts. Level 4 Evidence (Expert Opinion) is critical to help NASA define the risk of osteoporosis because an increased incidence of age-related fractures (i.e., fragility fractures) was unsubstantiated by the end of the ISS era as a result of low subject number and the prolonged time before fractures might occur.

The Bone Summit panelists were also asked to evaluate NASA's current methods for monitoring the risk of premature fractures in astronauts after space flight—fractures that may occur years later in life—, to provide their respective opinions as to which skeletal measures they consider necessary to monitor the risk for premature osteoporosis, and to evaluate the efficacy of in-flight countermeasures. The panel informed NASA (1) that the limitations of the DXA instrument itself prevented the test from fully capturing the effects of space flight, (2) that a research technology (Quantitative Computed tomography -QCT) revealed distinct effects of space flight on bone sub-regions of the hip that DXA could not, (3) that there is both delayed recovery and further loss of bone mass after space flight that are not detected by DXA, and (4) that finite element modeling of astronaut QCT data might inform individualized risk assessments for clinical decisions and should be further studied.

The opinions and interpretation of astronaut data for clinical relevance, or lack thereof, and for bone health management were published (Orwoll, 2013). The panel that had convened for the 2010 bone summit reconvened in 2013 and in 2016, with their role evolving into that of a Research and Clinical Advisory Panel (RCAP). The current Evidence Report is updated to convey the opinions of the summit panel's/RCAP's interpretation of the biomedical data and its assessment of the osteoporosis risk. As data continues to accumulate from astronauts who participate in long-duration missions, experts and additional consultants on bone loss and osteoporosis convene triennially to review QCT data and other bone relevant data (Bone Summit 2013 and Bone RCAP 2016); the aim of these reviews is to ensure that QCT is providing useful knowledge and to refine previously suggested protocols if required. The summarized assessments by these clinical experts are included as addenda to this Evidence Report.

III. INTRODUCTION

III.1 Description of Osteoporosis

The risk for early onset osteoporosis due to space flight is one of the more poorly understood health risk to astronauts. There is minimal baseline knowledge of skeletal health in the young, healthy, physically fit, predominantly male population that is exposed to the novel set of risk factors associated with the space environment and mission operations.

Osteoporosis is a skeletal condition that typically manifests with advanced age. It is characterized by several features of a deteriorated skeleton that collectively compromise the integrity of bones and increase the propensity of fracture in individuals who have encountered little or no trauma. The most recognized properties of osteoporosis are low aBMD and disrupted cancellous bone microarchitecture. The National Coalition for Osteoporosis and Related Bone Diseases states, "Although osteoporosis is not a geriatric disease, it may be seen as the geriatric consequence of a full life's worth of health predictors and behaviors, risks and choices; still, that message is not widely understood." This statement has great relevance to NASA as the space program attempts to understand space flight as a potential risk factor for osteoporosis in astronauts. One role of the HRP is to collect data that describes how the prolonged exposure to space flight may contribute to the premature manifestation of osteoporosis.

Since the Apollo era, astronaut testing has included evaluations of early technologies in bone densitometry (e.g. single photon absorptiometry), assessments of calcium balance, and assays of bone resorption biomarkers (i.e. hydoxyproline). These studies show increases in calcium excretion from bone and declines in bone mineral density specific to skeletal sites that are weight-bearing on Earth: this suggests that skeletal atrophy is occurring in space. The site-specificity of bone mineral density loss is thought to be driven by the change in load-bearing function from Earth's 1G environment to the weightlessness of space.

In 1994, the WHO developed clinical guidelines from aBMD measurements to diagnosis osteoporosis in postmenopausal women. These guidelines helped physicians identify menopausal women who require an intervention for fracture (WHO Technical Report Series, 1994). Subsequently, NASA realized this evidence-based clinical test for osteoporosis might help determine if space flight induces osteoporosis, and if astronauts require protection of skeletal health during space flight. The WHO Osteoporosis guidelines (c. 1994) (Table 1) reference aBMD measurements of osteoporosis patients to measurements obtained from a population of young white females. These epidemiological based WHO guidelines substantiate that persons with T-scores less than or equal to -2.5 (i.e. 2.5 standard deviations below the group mean BMD in healthy females) have a greater association with fragility fractures and would more likely benefit from a prophylactic treatment for bone mineral loss.

In general, Osteoporosis can be broadly divided into 2 categories that are based on different etiologies of skeletal deterioration: Primary osteoporosis ("involutional osteoporosis") is a consequence of the aging process (Riggs, 1998), whereas secondary osteoporosis is the deconditioning of the skeleton induced by factors other than aging, such as chronic glucocorticoid intake or metabolic diseases that induce bone loss. There are 2 types of primary osteoporosis: Type 1 postmenopausal osteoporosis and Type 2 senile-induced osteoporosis. Whereas the onset of primary osteoporosis (Type 1 and 2) might be specific to sex and age, secondary osteoporosis is not age-dependent. The overarching hallmark for primary or secondary osteoporosis is the occurrence of fractures after little or no trauma. The exposure to space flight may be a risk factor for secondary osteoporosis, but currently is only a putative risk factor because an increased risk for fractures due to space flight has not been proven in the astronaut cohort.

The collective aim of the HRP research gaps and tasks for Risk of Early Onset Osteoporosis is to describe the effects of space flight on multiple attributes of bone tissue and to determine how those changes affect the biomechanical integrity of bone (i.e. bone fragility). Areal BMD is a widely-applied method for detecting bone fragility, not necessarily because it is an accurate measurement of bone strength, but because there is an abundance of epidemiological data that link aBMD with fracture outcome. Specifically, DXA measurement of aBMD produces 2-dimensional images of bone mineral, but fails to capture any changes to 3-dimensional structure. However, as a clinical test, DXA measurement of aBMD is extremely useful: it is affordable and readily available; it has good precision; the radiation exposure is low and safe; scans can be performed quickly and can measure multiple skeletal sites simultaneously or specific skeletal regions (the hip and lumbar spine) accurately. Because of its utility, DXA has been applied to a multitude of studies on aging populations, clinical trials, and prospective studies with fracture outcomes–thereby making aBMD the best available predictor of fragility fracture.

However, clinicians use the aBMD-based guidelines (Table 1) to diagnose populations at risk for primary osteoporosis. Age-related bone loss is due to specific perturbations to bone remodeling that lead to net bone loss, an aspect of primary osteoporosis. The DXA measurement of aBMD, however, may not be as sensitive or as specific for the "complicated" subject with atypical bone loss that is due to factors unrelated to growing old (Seeman, 1992). Consequently, space flight-induced osteoporosis is more representative of a rare syndrome that mandates a better definition of skeletal changes (beyond the measurement of aBMD) to enhance a probabilistic assessment of fracture—which is the outcome of interest (not bone loss).

More than 15 years ago, osteoporosis experts recognized that a complete evaluation of fracture risk required supplementing the DXA measurement of aBMD with an index of Bone Quality (NIH Consensus Panel, 2001). The assertion has been undergirded by observed declines in the sensitivity and specificity of DXA aBMD to predict fragility fractures among the elderly (Schuit, 2005; Sorney-Rendu, 2007). In one report, up to 50% of persons with fractures had BMD T-scores in the normal or low bone mass range ("osteopenia") (Schuit, 2005).

WHO Classification	T-score (SD from mean BMD of young Caucasian females)
Normal	-1 to + 1
Osteopenia	Between -1 and -2.5
Osteoporosis	-2.5 or less
Severe Osteoporosis	-2.5 or less and fragility fracture

Table 1. WHO Guidelines for diagnosis of Op by BMD. BMD is used to stratify individuals according to relative risk for fracture but is a poor predictor of who will fracture**.**

Although useful, the aBMD-based clinical test is likely not sufficient for assessing fracture risk or diagnosing osteoporosis in astronauts because the test was designed for patients undergoing bone loss related to aging. The experts who participated in the 2010 Bone Summit asserted that fracture risk management may require more sensitive or innovative technologies to detect all of the effects of space flight that may influence the integrity of bone (Orwoll, 2013). Specifically, a reduction in "bone strength" in the astronaut could cause bone to fail or fracture under previously resisted levels of mechanical loading. An expanded knowledge of space flight-

induced changes to skeletal sites (especially the hip and spine) is vital because astronauts are physically active (exposed to large range of high energy loading) and are exposed to a novel assault to the skeleton about which little is known. A fuller understanding of the skeletal changes in astronauts is critical to evaluate whether current terrestrial osteoporosis therapies might be viable mitigating countermeasures. The recommendations for managing and mitigating the risk for early onset osteoporosis that were expressed at the Bone Summit 2010 are available in a NASA internal document (NASA/TM 2016-219284), in a peer-reviewed journal (Orwoll, 2013), and have been further refined as a consequence of additional reviews (Appendix: Bone Summit II 2013 and Bone RCAP 2016) .

III.2 Bone Physiology Background Information

To determine how space flight might increase bone fragility (osteoporosis), it is important to recognize the complexity of bone physiology here on Earth. The skeleton is capable of renewing and repairing itself through a "remodeling" process by which one-tenth of the adult skeleton is replaced annually. Bone remodeling occurs in discrete packets of skeletal tissue, referred to as "bone remodeling units", where the removal and replacement of bone tissue is the result of well-orchestrated actions of bone-resorbing cells (osteoclasts) and bone-forming cells (osteoblasts). This cellular regulation ensures (1) the temporal formation of bone after the resorption of bone (a process known as "bone coupling") and (2) the spatial formation of a bone volume to replace completely the resorbed volume of space in the resorption pit or lacunae ("bone remodeling balance"). Any perturbation to this cellular process can disrupt balance in the bone remodeling unit resulting in a deficit or a gain of bone, which can change material properties of whole bone (Figure 1). Because there are 1-2 million bone remodeling units in the adult skeleton (Riggs, 2005), a negative balance of bone in each bone remodeling unit could induce a net loss of bone mass over time or may compromise the integrity of that bone.

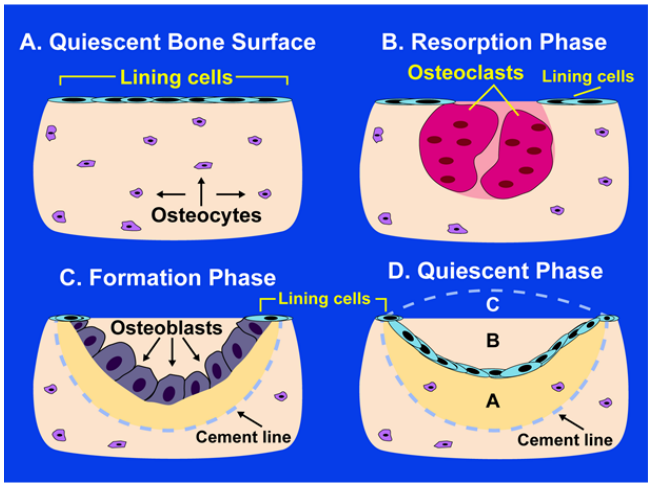


Figure 1. Remodeling of skeletal tissue at the level of the Bone Remodeling Unit. The remodeling process is a highly regulated mediation of cellular number and activities, initiated by cell signaling from osteocytes, to ensure that the removal and replacement of bone tissue occurs in a specific sequence (A through D) and at a specific tissue location. Any perturbation to this mediation (by local or systemic biochemical factors) can result in a resorption cavity that is under-filled, over-filled or equally-filled by new bone tissue. (Figure used with permission from R. Turner, Ph.D.)

Furthermore, the skeleton is composed of 2 types of bone: cortical bone (also known as compact bone) and cancellous bone (also known as trabecular bone or "spongy" bone). Eighty percent of the skeletal mass is composed of cortical bone, and the remaining 20% is cancellous bone. Cortical bone is found, for example, in the shafts of the long bones and in the endplates of the vertebrae; cancellous bone is found in the bone marrow compartments at the ends of long bones, within vertebral bodies and ribs, and in the pelvis. Ten percent of the skeleton is remodeled each year, but only 3% of cortical bone is renewed, whereas 25% of cancellous bone is renewed. This difference between cortical and cancellous bone turnover is due to the highly porous, scaffold-like structure of cancellous bone, which provides 80% of all bone surfaces in the skeleton. The first step of the remodeling process is bone resorption, and because osteoclasts are derived from a hematopoietic origin and can circulate throughout the body, the resorptive action of osteoclasts occurs on bone surfaces next to bone marrow and blood vessels. Thus, bone remodeling occurs predominantly in surfaces of cancellous bone, on the inside (endocortical) surface of cortical bone, and within cortical bone in Haversian canals. There are reports, however, of animal models that describe resorption occurring on the periosteal surface of cortical bone (Bliziotes, 2006). The vertebrae, the hip, and the wrist are more vulnerable to developing osteoporosis due to high content of cancellous bone and to cortical bone thinning. Incidentally, these same skeletal sites are most susceptible to fracture during activities performed on design reference space missions (DRMs) (Nelson et al, 2009).

It is well established that rates of skeletal remodeling are sex-specific. Figure 2 displays the different pattern of bone gain and loss in males and females as they age. This sex difference is primarily attributed to gonadal hormones, which influence multiple facets of bone volume regulation. Figure 2 depicts 3 phases of bone volume regulation in the aging population: bone mass gain (to peak bone mass) and bone mass loss (with menopause and with age).

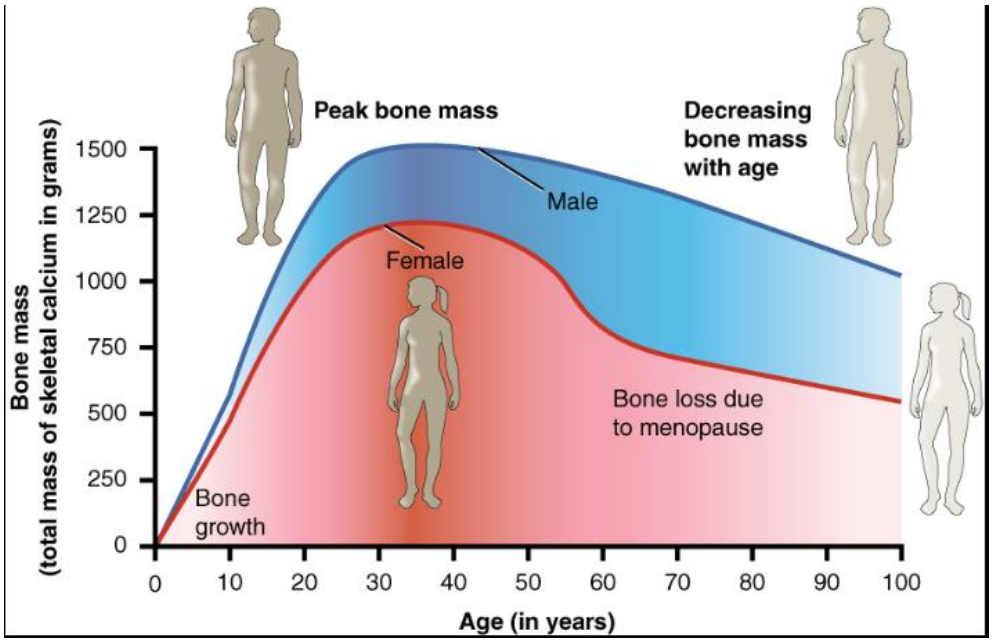


Figure 2. The pattern of involutional bone loss is displayed in this schematic of bone mass changes as the population ages. The pattern of bone loss diverges according to sex at around age 50 years; females undergo a biphasic loss while males experience a single phase of bone loss. With menopause, women lose bone at a rapid rate before experiencing senile bone loss at the same rate as men, which occurs at a slower rate. (Anatomy & Physiology. Connexions Web site. http://cnx.org/content/col11496/1.6/June 19, 2013).

Figure 2 displays how sex-specific skeletal growth occurs with the onset of puberty. The greater accretion of bone mass in males corresponds to androgen stimulation of radial bone growth, which results in bones with larger cross-sections. In contrast, estrogen in females suppresses radial growth, bone elongation, and expansion of the medullary canal. Age-related bone loss commences soon after peak bone mass is attained (~age 35) in both sexes. However, women undergo a biphasic loss of bone mass (with menopause and with age), whereas men experience only a single phase (with age) (Riggs, 1986). Since endogenous estrogen is capable of suppressing both the number and activity of the osteoclasts (Oursler, 2003), women are subjected to a rapid phase of bone loss with the onset of menopause at around age 50. Around age 70, women enter the second phase of bone loss (III); bone loss occurs at the same rate in both men and women and, in contrast to menopause, the age-induced loss of bone mass is slower as a consequence of a pervasive under-filling of remodeling units (Riggs, 2002; Riggs, 1998).

With menopause, the remodeling of bone tissue is accelerated, the "initiation rate" of bone remodeling units is high, and normal bone formation rates cannot replace bone tissue in resorption cavities quickly enough before the next remodeling cycle is initiated. The increased number of bone remodeling units can lead to increased porosity in cortical bone and to perforations of horizontal trabecular struts in cancellous bone microarchitecture. These changes to horizontal struts result in a loss of connectivity between trabeculae and a reduction in the mechanical strength of the trabecular scaffold, not unlike the collapse of a building as individual floors are destroyed by an implosion.

Aside from invasive analyses (e.g., bone histomorphometry of biopsies), the loss of bone mass by increased remodeling can also be inferred by detection of levels of biomarkers for bone formation and bone resorption (Garnero, 1999; Bonnick, 2006) in blood and urine, respectively. The relationship between biomarker levels and bone mass is not strong enough to diagnose osteoporosis in the individual (Melton, 1997), although assays of biomarkers are an established means of monitoring a response to osteoporosis therapy (Watts, 1999). Biomarkers reflect bone turnover, which is the generalized addition and subtraction of bone mass from the entire skeleton, and hence cannot be used to predict bone fracture at specific sites. Regardless, there is a new analysis method that might have value for simultaneously monitoring changes in bone formation and bone resorption through the detection of stable calcium isotopes; changes in the ratio of $Ca^{44/42}$ in small volumes of urine might provide a novel index for evaluating the in-flight skeletal response to interventions or countermeasures (Morgan, 2012; Smith, 2012b), though further validation studies are required to assess clinical utility (Gordon, 2014; Appendix C: Executive Summary Bone RCAP 2016).

Furthermore, perturbations in the endocrine regulation of bone volume accompany each phase of age-related bone loss. The increased release of calcium during menopause-induced bone loss initiates a cascade of down-regulated calcium-regulating hormones starting with the suppression of parathyroid hormone and the reduced production of 1,25-dihydroxyvitamin D; these endocrine responses can reduce the intestinal absorption of calcium from the diet. Over time, factors contributing to age-related bone loss, such as nutritional deficiencies and endocrinopathies, may induce hyperparathyroidism, a primary reduction of 1,25-dihydroxyvitamin D, and poor calcium absorption (Riggs, 1986).

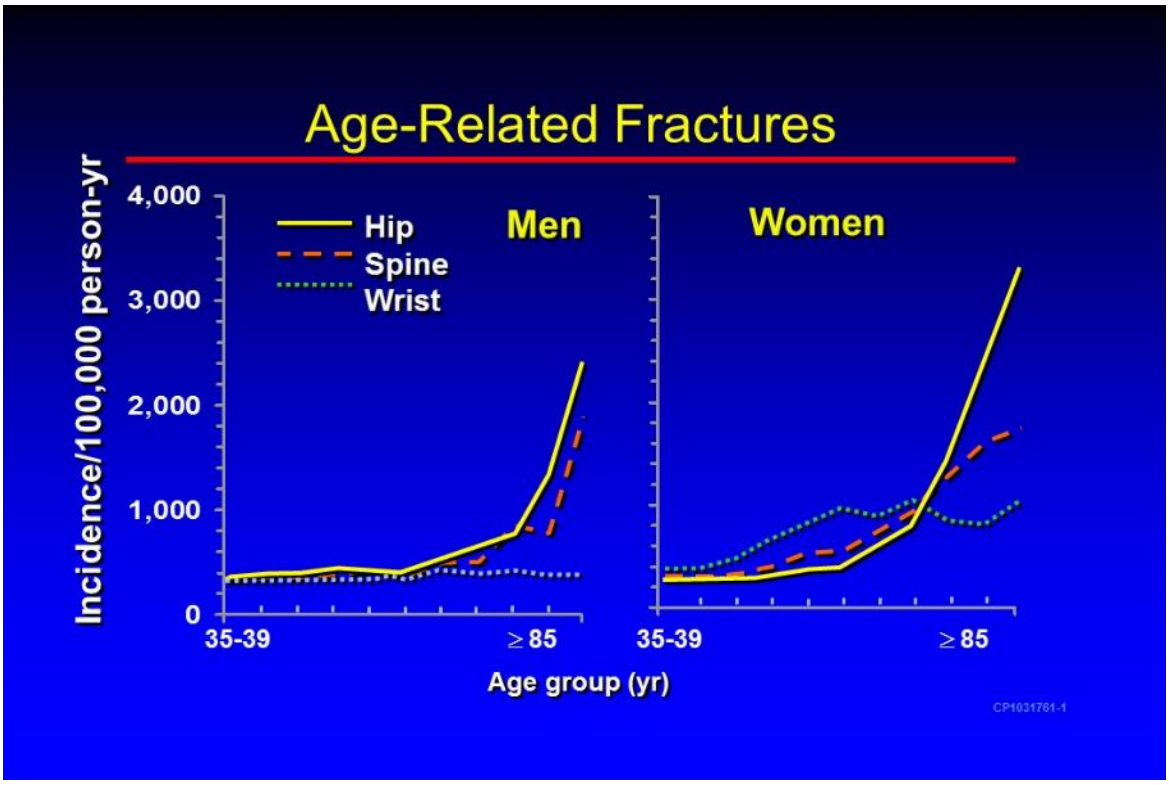


Figure 3. Age-related fractures in men and women. Women display an earlier and greater incidence of fractures at sites composed of predominately trabecular bone (Cooper & Melton, 1992) (Figure courtesy of S. Amin).

The phases of age-related bone loss (Figure 2) have specific characteristics that account for the different types and occurrence of fractures in men and women (Figure 3). Estrogen is a hormonal suppressor of osteoclastic resorption, and estrogen-deficient women display an accelerated turnover of bone with increased activation of bone remodeling units (a higher "birth rate" of remodeling new units or "activation frequency," as conveyed in Figure 4) and an unrestrained activity of osteoclasts (deeper and greater number of resorption lacunae, Figure 5).

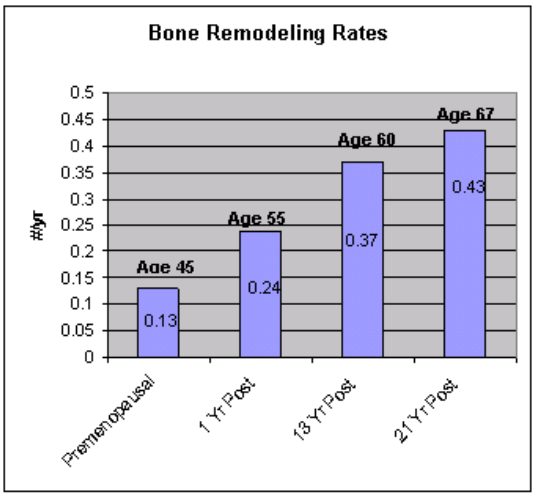


Figure 4. Bone remodeling rates, as determined by histomorphometric determination of activation frequency, increase with age (adapted from Recker, 2004).

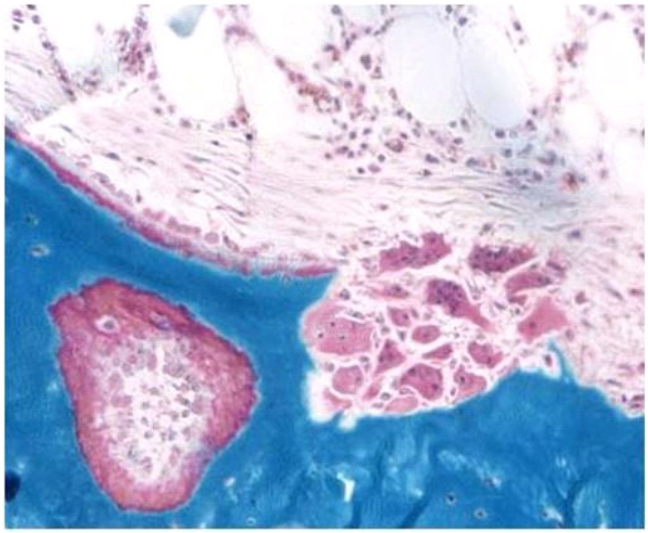
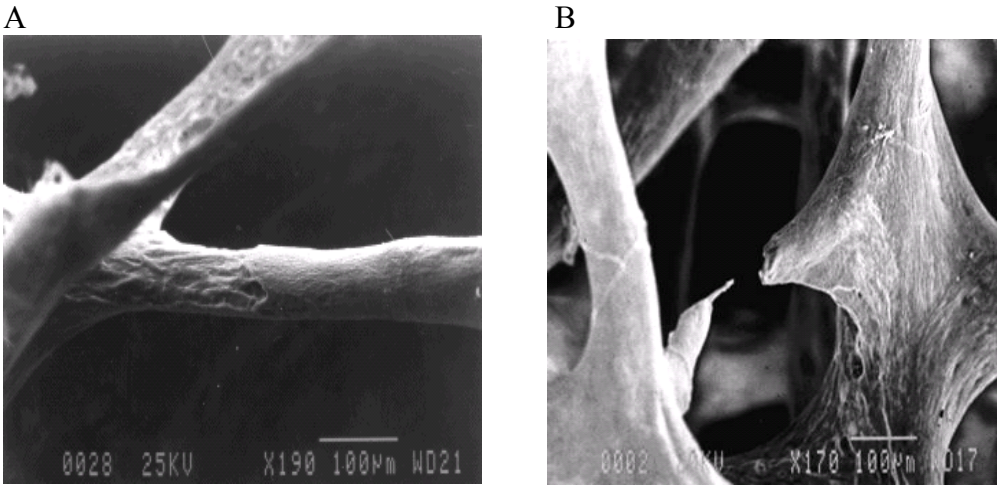


Figure 5. Unrestrained osteoclast recruitment and resorption of bone lacunae (slide courtesy of Mayo Clinic Bone Histomorphometry Lab).

As previously discussed, the rapid loss of bone with menopause preferentially occurs in the cancellous bone compartment (trabecular or spongy bone), where aggressive resorption occurs along the bone surfaces adjacent to bone marrow. This mechanism of bone loss leads to (1) thinning of the cortical bone shell and the trabecular plates (Figure 6a), (2) perforation of trabecular struts (Figure 6b), and (3) loss of trabecular elements and connectivity (Kleerekoper 1985; Mosekilde, 2000; Seeman, 2002).



Figures 6 a, b. Trabecular thinning and trabecular perforation as displayed by electron microscopy (Mosekilde, L).

A reduction in trabecular number and a reduction in trabecular thickness are microarchitectural changes associated with reduced mechanical strength (Figure 7) and the increased incidence of fractures (Figures 8). Overall, the rate of reduction in cancellous BMD is 3-5 times that of cortical bone density (3-4% BMD loss/year) and accounts for a higher incidence of fractures in women (compared to men of same age range) at skeletal sites predominantly composed of cancellous bone (wrist fractures and vertebral crush fractures) (Riggs, 1986).

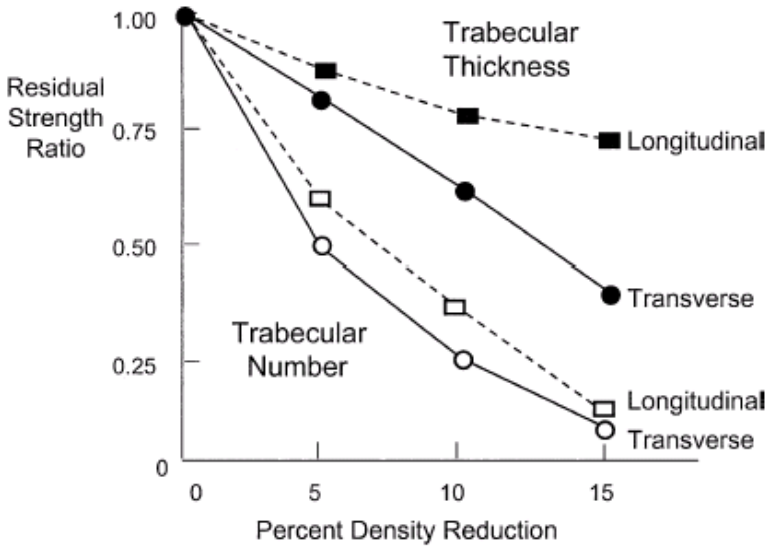


Figure 7. Changes in trabecular bone microarchitecture. Residual strength of cancellous bone compartment is less ("weaker") when density loss occurs by reduction in trabecular number ("linear" density of trabeculae) than by trabecular thinning (Silva, 1997).

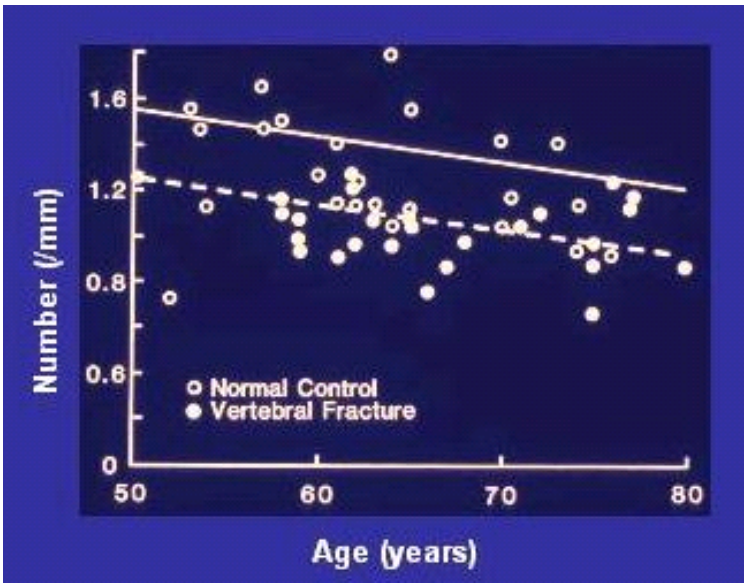


Figure 8. Reduction in trabecular number in bone microarchitecture is associated with fragility fractures (Kleerekoper, 1985).

Aggressive bone resorption that removes whole trabecular elements (reduced trabecular number) could lead to an irreversible loss in trabecular connectivity. In these cases, it would be critical to intervene with appropriate anti-resorptive therapy to prevent the disruption in bone microarchitecture.

Notably, the bone loss associated with age-related osteoporosis can involve both the cancellous and cortical bone compartments. With the under-filling of resorption cavities, the trabeculae of cancellous bone can become thinner; the thickness and total volume of cortical bone can be reduced, and the extent of porosity in cortical bone can increase. This reduction in bone mass, in both elderly men and women, may account for the greater incidence of fractures at the hip and wedge fractures in vertebral bodies of the spine.

Additionally, as women age, the skeletal effects of postmenopausal bone loss and age-related bone loss could combine. As shown in Figure 3, hip and vertebral fractures increase after age 70 in both sexes, but for women fracture rates start to increase slightly earlier and the prevalence of fracture is greater in woman than in men. More recently, QCT has been used to study populations (Riggs, 2004; 2008), and this more sensitive method substantiated that there are earlier (during gonadal sufficiency) and persistent losses in cancellous bone in both men and women (~33% and 50% of total lifetime loss, respectively). Women have substantial losses in cortical bone beginning around mid-life with the onset of menopause, whereas cortical bone loss in men did not accelerate until much later. Estrogen suppression of radial bone growth and bone elongation account for smaller bones in females, and female bones do not achieve the peak mass and size of male bones (Saeed, 2009). The loss of the anti-resorptive effects of estrogen during menopause results in enhanced osteoporosis rates (and its associated fragility fractures) in women compared to the osteoporosis rates in men of the same age.

Interestingly, there are some qualitative similarities between menopause-induced bone loss and space flight-induced bone loss. Common characteristics of "deficiencies" in estrogen and mechanical loading include

- Reductions in bone mineral density
- Rapid rates of bone resorption
- Declines in bone volumetric densities and structure
- Preferential trabecular bone loss
- Reductions in bone strength
- Perturbed endocrine regulation

Atypical changes observed with space flight and in healthy, young persons includes

- Increased bone resorption with uncoupled bone formation response (depressed)
- Reductions in bone mineral density targeted to weight-bearing bones
- Accelerated rates of bone loss and delayed recovery in hip trabecular bone
- Reductions in bone mineral density in males, especially at sites rich in trabecular bone
- Increased excretion of calcium with stable or reduced parathyroid hormone

At this time, there is no evidence for an increased incidence of fragility fractures in astronauts nor is there a clinical *fracture calculator*, e.g., FRAX, for predicting fractures in the young astronaut population exposed to the novel skeletal insult of space flight (Kanis, 2007). Hence, the goal of the current evidence report is to present skeletal data that describes space flight-induced changes that might increase the skeletal fragility of astronauts. In the absence of fracture evidence and a predictive test, the present report defines the osteoporosis risk in astronauts by presenting an analogy, i.e. the absence of gravity in space may predispose astronauts to early onset osteoporosis, just as the deficiency of estrogen does for the female sex.

IV. EVIDENCE

IV.1 Data Obtained from Space Flight Medical Operations

DXA measurement of aBMD (g/cm^2) is a widely-applied clinical test for diagnosing osteoporosis in the aging population. Active and retired astronauts undergo DXA regional scans of the hip and spine (in addition to whole body, forearm, and calcaneus scans) on a triennial basis. The guidelines for diagnosing osteoporosis (based upon aBMD T-scores, Table 1) are used to monitor skeletal health throughout an astronauts' active career in the space program and after retirement. DXA scans are performed on ISS astronauts before and after flight to document changes in aBMD (g/cm^2) as a percentage change from baseline (preflight) measurement. Changes in DXA scan values describe the effects of space flight (changes preflight to immediate postflight), the changes associated with re-ambulation after return to Earth, and the mitigating effect of various in-flight countermeasures to bone loss that are assessed in research studies.

IV.1.1 Areal Bone Mineral Density (aBMD) by Dual-Energy X-ray Absorptiometry (DXA) – T scores

The WHO (Table 1) use aBMD T-scores to set ranges of values that provide a guideline of relative risk for fractures due to osteoporosis (i.e., fragility fractures). As previously discussed, a T-score represents the number of standard deviations the astronaut's aBMD is from the group mean aBMD in young healthy white females. NASA adapted the WHO guidelines to set standards for bone health in ISS astronauts (Sibonga, 2016). NASA adapted clinical guidelines for osteoporosis diagnosis (determined from measurements at the hip and lumbar spine) to drive clinical decision-making, to set medical standards (NASA STD 3001) for human health and performance, and to establish a level of efficacy for in-flight countermeasures. The medical standards for astronaut health establish the minimum level of skeletal health that an astronaut must attain before a space flight mission (fit-for-duty criterion) and a permissible outcome limit for skeletal health after a mission as denoted in Figure 9. Countermeasure efficacy is determined by the countermeasure's ability to keep the astronaut above the non-permissible outcome limit (i.e. T-score > -2.0 for the hip and spine).

Astronaut's aBMD T-scores before and after an ISS missions (Figure 9a) suggest that the fit-for-duty standard for a long-duration missions is sufficient to keep the hip and spine post-mission T-scores $\geq$ -2.0 after return from a mission. However, the clinical data also indicate that an astronaut could lose up to 1.5 SDs during flight (1.5 T-scores)—which could represent as much as a 25% decline in aBMD—and still be in the accepted skeletal health range after return. Moreover, the clinical index used by the flight surgeon to evaluate the astronaut's risk for fragility fractures is not responsive to in-flight countermeasures (e.g., bisphosphonates and resistive exercise on ARED), although these countermeasures clearly reduce the typical decline in aBMD seen after prolonged space flight (Smith, 2012a; LeBlanc, 2013). Thus, the utility of aBMD T-score to assess the risk for osteoporosis relative to the changes during space flight or the effectiveness of countermeasures to bone loss, is not apparent.

DXA measurement of aBMD is conducted more frequently as a medical requirement (before and after space flight, and postflight until recovery) but only on crewmembers who flew on long-duration missions, i.e. as previously mentioned, those serving on space flight missions >30 days but typically > 6-months.

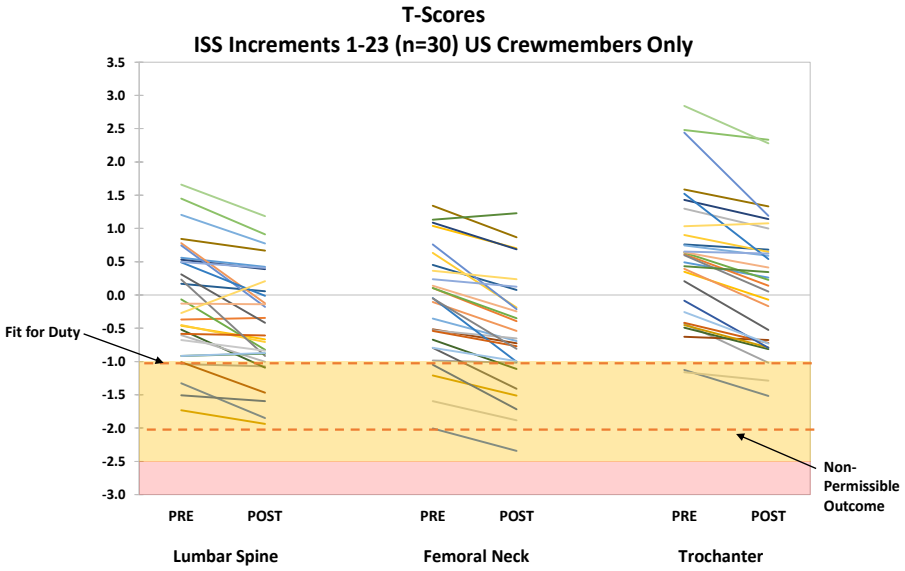


Figure 9. Thirty sets of preflight and postflight measurements (n=30 missions) from 28 different US astronauts (2 astronauts participated in 2 missions). Preflight and postflight T-scores are superimposed on the WHO diagnostic guidelines for osteoporosis (Diagnosis: T-scores > -1.0 denote normal; pink shade denotes osteoporosis; yellow shade denotes low bone mass/osteopenia) developed for perimenopausal and postmenopausal women, and men over the age of 50. These diagnostic criteria were the only evidence-based guidelines available for evaluating skeletal integrity when BMD measurements by DXA became the medically-required test for astronauts (NASA Med Vol. B). The one crewmember who returned with a T-score less than the permissible outcome limit of -2.0 had flown very early in the ISS program.

IV.1.2 Areal BMD by DXA – Z-scores – Comparison to Age-matched Terrestrial Population

The aBMD T-score is used to diagnose primary osteoporosis, whereas the Z-score tells the flight surgeon how many standard deviations (SDs) a crewmember's DXA-measured aBMD value is relative to the group mean value for an age- and sex-matched reference group. Hence, the Z-score provides an index to evaluate whether an astronaut's aBMD is in the expected range for his or her age (Figure 10). The Z-score is not used to diagnose primary osteoporosis (age-related) although it has been suggested that a Z-score less than -2.0 might trigger further evaluation for secondary osteoporosis; however, this convention is not substantiated by data. In other words, there is no study to validate that a Z-score < -2.0 is associated with a higher rate of metabolic bone disorders or that secondary causes (e.g., chronic glucocorticoid-induced fractures) do not occur in persons with Z-scores > -2.0 (Seeman, 1982).

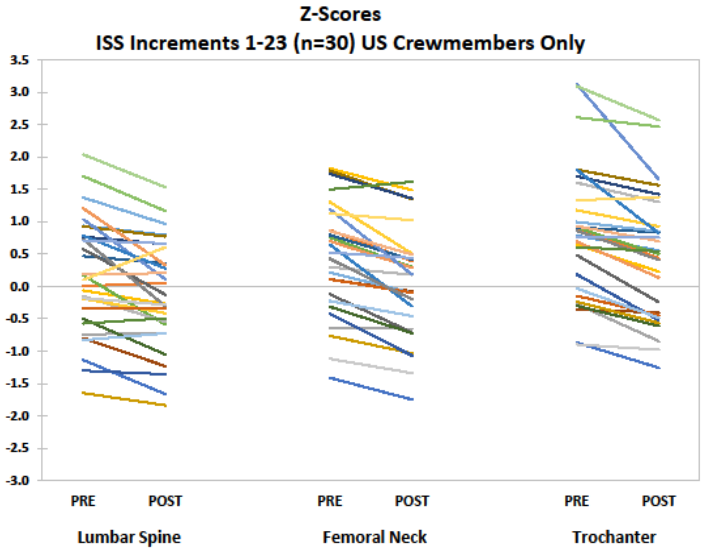


Figure 10. The Z-score compares the US astronaut aBMD values to a sex- and age-matched reference dataset to evaluate consistency with values in peer age-group. The Z-score does not integrate the effect of age on fracture risk (IP=International Partners).

IV.2 Data Obtained from Scientific Investigations in Flight

IV.2.1. Skeletal Data acquired by Dual-Energy X-ray Absorptiometry (DXA)

2.1.1 Space flight Data

DXA technology has been used as a research modality to describe the space flight induced bone changes as percentage loss of preflight aBMD. DXA technology was used to measure aBMD (g/cm^2) of cosmonauts serving on the Mir spacecraft. LeBlanc et al. (2000) reported DXA data from crew (n=16-18, a complete dataset was not available in all cosmonauts) before and after space flight missions aboard the Mir spacecraft. A change in aBMD was calculated over an entire mission. However, because of the wide range of mission durations (~4 to 14 months), aBMD losses were normalized to months of space flight. An averaged loss was 1-1.5% aBMD per month (Table 2). Further assessment revealed large variability in aBMD losses in crewmembers, both inter-skeletally and intra-skeletally. In addition, aBMD losses were greater in the lower limbs, and the hip and spine of the central skeleton, i.e., weight-bearing sites that also have a high incidence of osteoporotic fractures in the elderly population on Earth. As a consequence of this research study of Mir crewmembers, DXA measurement of aBMD is currently required before and after space flight, but only for crewmembers serving on space flight missions >30 days (i.e., not for crewmembers flying aboard the Space Shuttle which are spaceflights less than 30 days).

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BMD and Body Composition Changes after 4-14.4 Months of Space Flight			
Variable	**N**	**% / Month Change**	**SD**
BMD Lumbar Spine	18	-1.06*	0.63
BMD Femoral Neck	18	-1.15*	0.84
BMD Trochanter	18	-1.56*	0.99
BMD Total Body	17	-0.35*	0.25
BMD Pelvis	17	-1.35*	0.54
BMD Arm	17	-0.04	0.88
BMD Leg	16	-0.34*	0.33

Table 2. Change in BMD (averaged change per month) in crew members serving on missions on the Mir spacecraft (LeBlanc, 2000). The data represent declines in aBMD before bisphosphates or resistive exercise on the ARED were available.

In 2008, an advanced resistive exercise device (ARED) become operational on the ISS. This device provides resistive forces up to 600 lbs. Weight-bearing exercises are more beneficial to bone health than exercises for aerobic conditioning (Khort, 2004) and pound forces of 2-3x body weight for skeletal loading is considered optimal for skeletal health (Perusek & Myers; After Action Report). ARED exercise loading of weight-bearing skeletal sites (hip and spine) has reduced the declines in aBMD from 1-1.5% to 0.3-0.5% of preflight aBMD per month (Sibonga, 2016; Smith, 2012).

2.1.2 Comparison to Terrestrial Aging Populations

When the 0.3-0.5% averaged monthly loss of aBMD in crewmembers performing resistive exercise on the ARED are normalized to yearly loss (3.6-6.0%), the total loss exceeds the 2-3% averaged loss of aBMD per year in vertebrae of postmenopausal females during the first decade after onset of menopause—characterized as a precipitous bone loss (Riggs, 1986). A 0.5-1% loss per year is detected in comparable skeletal sites in older persons, i.e., onset of senile osteoporosis (Orwoll, 2013). Figure 11 a, b provides a comparison of longitudinal changes in total hip aBMD as a function of age for both men and women as reported by Warming (2002); data derived from crewmembers who participated in ISS missions or missions on the Russian Mir spacecraft are superimposed on the Figure 11. The changes in aBMD in the terrestrial population were measured over a 2-year period, whereas the averaged aBMD changes in astronauts were measured over mission periods that typically lasted 6 months. Hip aBMD losses after a 6-month space flight mission (Figure 11 a, b) in male astronauts aged 35-55 years were ~6-fold greater after space flight than the losses incurred over 24 months in men of comparable age. Comparisons of age-related losses in aBMD were also conducted for the clinically relevant sites of forearm and spine; male crewmembers displayed large variability in aBMD loss in the lumbar spine and forearm (data not shown). This comparison between astronaut and terrestrial populations indicates that space flight induces a loss of aBMD that is rapid and exceeds the normal loss in aBMD over the same duration in a similarly-aged terrestrial population.

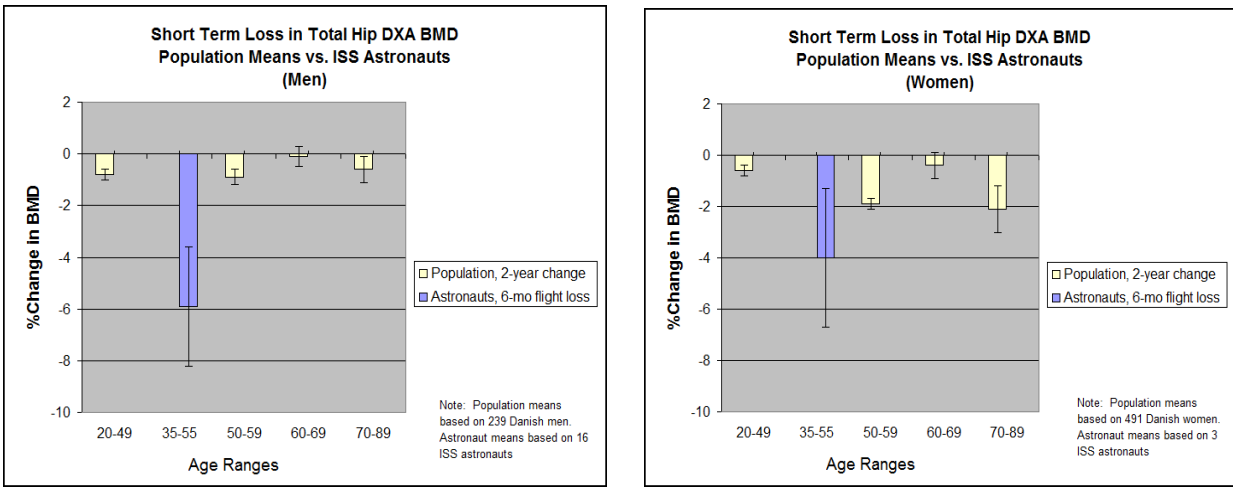

Figure 11 a, b. Comparison of BMD change for total hip in male (a) and female (b) crew members vs. population mean. ISS: International Space Station. (Adapted from Warming, 2002, and Johnson Space Center Bone Mineral Lab).

Overall, space flight induces a loss of aBMD that is targeted to weight-bearing skeletal sites, and is greater than aBMD loss for comparable sites in non-flying persons of similar ages over the same time period. Moreover, the loss rate for aBMD during 6 months in space may be even greater (i.e., faster) than the accelerated loss rate observed in females soon after the onset of menopause—the accelerated rate of loss during menopause in females is associated with weakened bone structure and premature fragility fractures for the female sex relative to fracture onset in men.

In addition, an epidemiological analysis of astronaut data, conducted at the Mayo Clinic, evaluated how the observed loss of aBMD in astronauts compares to the expected loss of aBMD in an aging terrestrial population-- for identical skeletal sites and estimated over the same period of time. Specifically, the Rochester Bone Health study (Rocca, 2012) is an aging population cohort in southwestern Minnesota with subjects ranging between 20-97 years of age (n~800 subjects, 1:1 males to females); this cohort is one of the few, if not the only, study cohort to study skeletal health that includes subjects of younger ages (150 men and 150 female subjects between the ages of 20- 50 years). An algorithm was derived (from longitudinal aBMD measurements performed in subjects of the Rochester Bone Health) to predict changes in aBMD over a given period of time. Moreover, the epidemiological study also evaluated which preflight risks factors for bone loss (established and putative risk factors) might be predictive of aBMD loss during spaceflight and recovery after return in astronauts.

As shown in Table 3a, aBMD data obtained from male and female astronauts before and after long-duration space flight (n=32, except for wrist – n=24) were applied to the algorithm. The algorithm revealed that the mean bone loss in the group of astronauts immediately after space flight and at ~12 months after return to Earth was significantly greater than what is expected for the terrestrial Rochester population (Amin, 2010). Declines in the hip and spine were noted in male astronauts following long-duration missions (n=14) -- the hip and spine being clinically-relevant skeletal sites for developing osteoporosis in terrestrial aging populations; Table 3b

suggests that such changes in the hip can persist up to 3 years after return from a mission (Amin, 2011).

	Mean BMD (g/cm²) (% change in BMD per month) [95% Confidence Interval]					
BMD Site	**Immediate Post Flight**			**~12 Month Post Flight**		
	Predicted	**Observed**	**p-value**	**Predicted**	**Observed**	**p-value**
Total Hip	1.082 (-0.00) [-0.05, 0.04]	1.012 (-0.87) [-1.04, -0.71]	<0.001	1.086 (0.01) [-0.01, 0.02]	1.062 (-0.10) [-0.15, -0.06]	<0.001
Spine	1.078 (0.12) [0.10, 0.13]	1.028 (-0.48) [-0.61, -0.34]	<0.001	1.086 (0.05) [0.05,0.06]	1.068 (-0.03) [-0.01, 0.03]	0.004
Ultradistal Radius	0.519 (-0.02) [-0.05, -0.00]	0.511 (-0.21) [-0.34, -0.09]	0.01	0.512 (-0.07) [-0.07, -0.06]	0.517 (-0.02) [-0.07, 0.02]	0.03
Mid Shaft Radius	0.710 (0.17) [0.11, 0.23]	0.695 (-0.06) [-0.17, 0.04]	0.001	0.705 (0.06) [0.03, 0.09]	0.694 (-0.01) [-0.06, 0.04]	0.02
Total Body	1.264 (-0.05) [-0.05, -0.04]	1.240 (-0.26) [-0.37, -0.16]	0.002	1.264 (-0.02) [-0.03, -0.02]	1.248 (-0.08) [-0.15, -0.01]	0.08

Table 3a. Observed (from 32 combined astronauts, Males 26, Females 6) and predicted aBMD changes (from algorithm) based upon aBMD data acquired immediately (n=32) and approximately 12 months (n=28) after return from long-duration flights (Amin, 2010).

BMD Site	**Mean Immediate Post Flight BMD (% change/month)**			**Mean Three Year Post Flight BMD (% change/month)**		
	Predicted	**Observed**	**p-value**	**Predicted**	**Observed**	**p-value**
Total Hip	1.063 (0.05)	0.994 (-0.76)	<0.001	1.066 (0.02)	1.047 (-0.03)	<0.001
Lumbar Spine	1.081 (0.11)	1.016 (-0.58)	<0.001	1.085 (0.03)	1.069 (-0.00)	0.11
Ultra-Distal Radius	0.558 (-0.05)	0.550 (-0.20)	0.12	0.541 (-0.08)	0.551 (-0.04)	0.005
Mid-Shaft Radius	0.755 (0.19)	0.741 (-0.00)	0.04	0.749 (0.02)	0.741 (0.00)	0.28
Total Body	1.288 (-0.04)	1.262 (-0.26)	0.009	1.284 (-0.01)	1.261 (-0.05)	0.19

Table 3b. Observed and predicted BMD changes in male astronauts immediately and approximately 3 years after return from a long duration mission (Amin, 2011). Data not shown for females.

Declines in aBMD for the clinically-relevant sites of the hip, lumbar spine and mid-shaft radius were detected in male astronauts immediately after space flight. The observed declines were significantly different from the declines predicted, for same period of time, in a sex-matched, terrestrial aging cohort. Additionally, the mean hip aBMD for the same male astronauts, measured at 3 years after the mission remained significantly lower than the values predicted by the algorithm derived from the Rochester cohort; this latter observation suggests that astronauts might be at risk for hip fractures even 3 years after a mission (Amin, 2011). The astronauts analyzed in this study did not have access to the ARED; an analysis using data from ARED users is in progress.

Notably, there are no studies of populations, especially those covering the age range of active astronauts (35-55 years), that relate *changes* in DXA aBMD to fracture outcomes (presumably because there are very few fragility fractures in this age group–Kanis, 2001). Moreover, the clinical guidelines for osteoporosis diagnosis are based upon T-scores (See Figure 9) and the T-score assessments may not be useful for evaluating the effects of space flight on skeletal health (See Appendix. Bone Summit Executive Summary, 2013). Hence, a criterion for assessing countermeasure efficacy relevant to the ages of the astronaut cohort and for capturing the full effects of space is a prominent HRP GAP (see Section VII GAPs).

In spite of its limitations, DXA is considered the most clinically-useful medical test for assessing relative fracture risk. This utility is not because of its accurate assessment of bone, but because of its extensive application to studies of aging populations and its use in clinical trials of osteoporosis therapies. Consequently, there is an abundance of epidemiological data that associates aBMD to fracture outcome. However, DXA technology cannot detect changes in three-dimensional whole bone structure, or changes in separate compartments of whole bone (cortical vs. trabecular bone), a limitation that might account for the DXA's reduced specificity and sensitivity in predicting fractures in individuals (Schuit, 2004; Sornay-Rendu, 2005; Wainright, 2005). This limitation might also limit fracture assessment for conditions or countermeasures that might differentially impact sub-regions of bone, such as space flight (Lang, 2004; Carpenter, 2010), pharmaceuticals (Keaveny, 2008; Chestnut, 2005), or exercise (Adami, 1999; Haapasalo, 2000; Hind, 2011; Schipilow, 2013; Liphardt, 2015). Thus, to fully understand the space flight effect on bones and thereby on fracture probability, sensitive techniques and analyses might be needed to monitor the effects on separate hip bone sub-regions (and other associated morphological indices) (Oganov, 1990). Moreover, it might be necessary to conduct QCT scans in addition to DXA for assessing recovery in cortical and trabecular compartments after space flight, providing information that could trigger intervention (Orwoll, 2013). Current astronaut data suggests that risk management should initially focus on the surveillance of structural deficits to the hip, and on whether in-flight countermeasures can effectively mitigate changes to this site (Lang, 2004, 2006; Orwoll 2013). HRP is also developing and evaluating technologies and tests that survey the spine and can be used clinically to manage vertebral fragility in astronauts.

IV.2.2. SKELETAL DATA ACQUIRED BY QUANTITATIVE COMPUTED TOMOGRAPHY (QCT)

2.2.1 Space flight Data

There is evidence that space flight-induced remodeling is specific to separate bone compartments, and can be delineated by QCT scans of hip and spine. QCT technology and peripheral QCT have detected greater losses in volumetric BMD [vBMD] of cancellous bone compartments than in cortical bone compartments (on basis of percentage change from preflight measurements) in both Russian and U.S. crew who participate in long duration missions (Vico, 2000; Lang, 2004). The influence of vBMD loss (as determined by QCT measurements) on fracture incidence in the relatively young astronauts might never be determined given the small number of individuals and the many years required for follow-up. Still, QCT is useful for detecting space-flight-induced changes to 3-D structural attributes not detectable by 2-D DXA assessments.

QCT scans performed on the spine and the total hip (femoral neck and proximal femur) of crewmembers serving 6-month missions on the ISS quantified trabecular bone losses of 2.2-2.7% per month (Lang, 2004) in the hip and 0.7% per month in the lumbar spine, as averaged to month of duration (n=14 crewmembers) (Table 4).

QCT Changes in BMD in 14 ISS Crewmembers (%/Month±SD)	
Lumbar Spine, Integral	-0.9±0.5**
Lumbar Spine, Trabecular	-0.7±0.6*
Total Hip, Integral	-1.4 ± 0.8 **
Total Hip, Trabecular	-2.3±0.8**
Femoral Neck, Integral	-1.2±0.7**
Femoral Neck, Trabecular	-2.7±1.9**

Table 4. Changes in volumetric BMD for combined cortical and cancellous bone compartments ("integral") and for trabecular bone compartment of the lumbar spine, total hip, and femoral neck. Significant reductions occurred in volumetric BMD, expressed as loss averaged per month, for all sites with greater percentage deficit for trabecular bone of proxmal femur (Lang, 2004, Orwoll 2013).

For the total hip and femoral neck, the percentage vBMD loss was greater in the trabecular compartment (the more metabolically-active site) than in the combined compartment (cortical + trabecular = "integral"). However, on the basis of total mass, vBMD loss was greater in the highly dense cortical bone than cancellous bone due to loss from the endocortical surface (Lang, 2004) and possibly from intra-cortical porosity, although intra-cortical porosity is not directly discernable by QCT. These structural changes at the femoral neck represented a reduction in both estimated axial compressive strength and bending strength (Lang, 2004). There was no difference in compartment-specific changes in the integral vs. trabecular bone compartments of the spine.

QCT technology can detect these skeletal changes, whereas DXA technology cannot; however, QCT does not have the resolution to assess how loss in the cancellous bone compartment affects the microarchitecture of trabecular bone. Space-flight-induced changes to trabecular microarchitecture (e.g., trabecular thinning or loss of trabecular connectivity) for sub-regions of the hip and of the spine are unknown, in part due to limitations in non-invasive technologies. However, European Space Agency (ESA) has assessed 13 cosmonauts with high resolution peripheral QCT (HR-pQCT, Scanco) and reported space flight-induced changes to the wrist and ankle (Vico, 2015). Relative to the weight-bearing distal tibia (at the ankle), the distal radius of the wrist did not appear to lose bone mass during a 6-month ISS mission; however, declines in cortical bone thickness and the failure load of the distal radius (i.e., its ultimate strength) were detected 3, 6, and 12 months after flight. Moreover, trabecular bone mass appeared to decline after return to Earth, resulting in a deficit 12 months later. For the distal tibia, space-flight-induced losses in cortical thickness were recovered within 12 months of return to Earth, but deficits in bone mass and ultimate load of trabecular bone persisted (Vico, 2015). The "T-bone" study, sponsored by the Canadian Space Agency, is testing crewmembers with an updated model of HR-pQCT (62 micron resolution). This study is in progress with data collection expected to be complete by 2020.

2.2.2. Comparison to Terrestrial Aging Population

QCT was used to determine age- and sex-differences in the vertebra and proximal femur in a population of men (n=323) and women (n=373) aged 20-97 years (Riggs, 2004). Conventional QCT measurements of whole bone geometry and volumetric BMD, were used to characterize whole bone structure of the proximal femur, distal tibia and radius, and vertebrae of the lumbar spine. Albeit on the basis of cross-sectional group comparisons, effects of age and of sex on bone structure and on vBMD trends *before* midlife (i.e., during gonadal sufficiency) were revealed by QCT scans. The QCT outcomes (described below) enhance the DXA characterizations of age effects on the skeleton.

- Reduced vBMD of cortical bone, suggesting increase in cortical porosity
- Thinning of the cortex by resorption at the endocortical surface
- Declining rates in volumetric BMD specific to bone compartments (cortical vs. trabecular).
- Increases in cross-sectional area, suggesting an outward displacement of cortical bone

In females, the reduction in trabecular bone is roughly 3-5 times greater than the loss of cortical bone and accounts for the greater incidence of fractures in the wrist and spine (trabecular rich skeletal sites) in women -- relative to men -- during the early years after menopause onset (see Figure 2). Histomorphometry of bone biopsies of postmenopausal females indicates that there is an increased number of osteoclasts with aggressive resorptive activity leading to the perforation of trabecular plates and loss of trabecular elements (i.e., loss of connectivity) (Parfitt, 1983). Reductions in trabecular elements are correlated with fractures and reduced whole bone strength in vertebral bodies (Kleerekoper, 1985; Van der Linden, 2001; Silva, 1997). Disruptions in trabecular microarchitecture in the hip have still to be fully defined.

Geometrical changes and trabecular bone losses observed with postmenopausal osteoporosis and with normal aging are *qualitatively* similar to those documented after long-duration space flight. There are differences, however, between bone loss induced by space flight and bone loss induced by aging (both postmenopausal and senile primary osteoporosis); specifically, there are differences in the rate of bone loss, the uncoupling of bone formation from bone resorption, and the targeting of bone loss to weight-bearing sites in astronauts, suggesting local mediation of spaceflight-induced bone loss, presumably biomechanical signals affecting bone cell number or activities.

MRI technology has successfully demonstrated clinical utility for detecting changes in trabecular microarchitecture of peripheral skeletal sites, i.e., the ankle and wrist (Wehrli, 2008; Carballido-Gamio, 2006; Chesnut, 2005). Furthermore, new MRI technologies with reduced signal-to-noise ratios are emerging that might be able to assess trabecular bone microarchitecture of deeply embedded bones (e.g., hip or spine). Clinical trials are still required to validate the clinical utility of these novel technologies, which have the added advantage of not using ionizing radiation (Folkesson, 2011; Hotca, 2015; Chang, 2015).

IV.2.3 DELAYED RECOVERY OF BONE LOSS

2.3.1 Space flight Data

2.3.1.1 DXA aBMD

Sibonga (2007) reported a novel method for analyzing aBMD to characterize skeletal recovery. BMD was measured over a post-flight period of 5 years. DXA BMD measurements (both cross-sectional and longitudinal) from 45 astronauts who participated in a total of 56 flights (4-14 months) were fitted to a 2-parameter exponential mathematical equation (Figure 12). A "half-life" index was derived that provided the timing of 50% restoration of BMD in days after return from space. Despite the large variability in the BMD measurements and the large variability in half-life values, the asymptotic increase in BMD over the post-flight period was clearly apparent, and provided the basis for the assertion that substantial recovery could occur at >4 times the half-life (Table 5) (Sibonga, 2007). Depending upon skeletal site, half-life values ranged between 3 and 9 months.

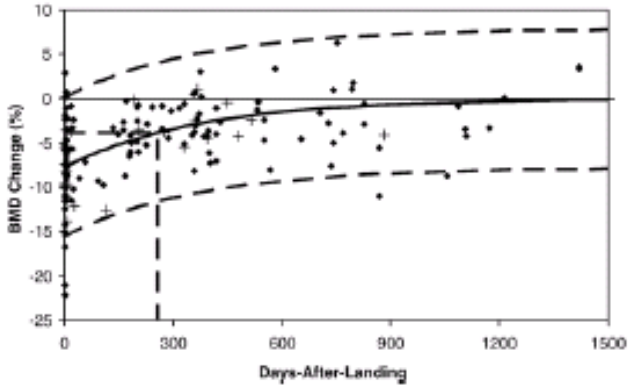

Figure 12. Changes in BMD at the trochanter after landing. The intercept of the fitted line shows where 50% recovery time for the 7.8% space flight-induced bone loss would occur after about 8.5 months (Sibonga, 2007).

Summary of fitted data per skeletal site

Skeletal site	Loss (L0) at landing %	50% recovery time (days)
Femoral neck	6.8 (5.7, 7.9)	211 (129, 346)
Trochanter	7.8 (6.8, 8.8)	255 (173, 377)
Pelvis	7.7 (6.5, 8.9)	97 (56, 168)
Lumbar Spine	4.9 (3.8, 6.0)	151 (72, 315)
Calcaneus	2.9 (2.0, 3.8)	163 (67, 395)

Table 5. Fifty percent recovery time represents the number of days after landing at which there is a restoration of half of the bone mineral lost during space flight. L_0 represents BMD loss as a direct consequence of space flight. Confidence limits (95%) for the fitted values are provided in parentheses.

Recently, analysis of skeletal recovery was updated to include DXA BMD data from ISS crewmembers dating back to ISS missions in 2005. Starting in 2008 the ARED (Advanced Resistance Exercise Device) has been available on the ISS, allowing astronauts to perform resistive exercises that more closely approximate weightlifting on Earth (Loehr, 2011). The updated analysis applied the mathematical fit to the expanded dataset and helped describe how the use of this higher fidelity exercise device influenced loss and recovery of BMD in ISS crewmembers.

Table 6 presents the recovery half-life and the loss in BMD in some of the astronauts who flew between 2005 and 2014. There are some differences in this updated analysis from the previously published report (Sibonga, 2007): (1) updated analysis focuses on BMD data from the lumbar spine and the total hip, in lieu of the trochanter and femoral neck; (2) the dataset includes eight additional females (from n=4 to 12); (3) because the aim was to assess the impact of the US ARED exercise on recovery pattern in astronauts, cosmonaut data were not included; and (4) trends in repeat fliers were not specifically evaluated.

Skeletal Site	**Loss (L0) at landing % (min, max) Pre-ARED vs. ARED**	**50% Recovery Time (days) (min, max) Pre-ARED vs. ARED**
Total Hip	6.0 (5.0, 7.1) vs. ARED 3.7 (2.4, 4.9)	229 (12, 327) vs. ARED 105 (0, 243)
Lumbar Spine	3.8 (2.4, 4.9) vs. ARED 3.2 (1.2, 5.2)	115 (16, 213) vs. ARED 62 (0, 255)

Table 6. The mathematical fit was applied as BMD data accumulated --some of which were acquired from ISS astronauts who performed resistive exercise on ARED. There was no overlap between the Confidence limits (95%) of the fitted values, as provided in parentheses, between Pre-ARED and ARED. This observation suggest that the availability of ARED hardware reduced the BMD loss in the total hip of astronauts. No influence of ARED on BMD loss in the lumbar spine or on the BMD recovery pattern for hip and spine can be determined at this time by the model.

Cosmonauts and the astronauts who took bisphosphonates were excluded from this analysis, and the updated analysis covered data from a total of 53 male subjects. The updated analysis of the data from these 53 male astronauts revealed a beneficial impact of ARED use (n=29) relative to non-ARED use (n=24) on reducing the amount of aBMD loss at the hip on the day of landing (i.e., no overlap in confidence intervals), but an effect on recovery could not be discerned. Although the number of female subjects in this study increased to 12, the data were insufficient to discern a trend with the fit to describe loss at landing (y intercept) and a recovery half-life (days after landing).

2.3.1.2 QCT Data

There is evidence that the recovery of space-induced bone loss is delayed in the post-flight period compared to the time it takes to lose the bone. Vico et al (2000) measured BMD using peripheral QCT shortly after landing and 6 months later, and failed to detect any recovery of BMD in the lower limbs of crewmembers who had spent 6 months in space, suggesting that recovery from space flight-induced BMD loss could take longer than the mission duration. Additionally, Lang et al. (2006 a) conducted QCT scans at the proximal femur in 11 ISS crewmembers a year after return from space flight, and compared the 1-year postflight scans to scans taken from the same individuals soon after landing. The cross-sectional volume (cm^3) of the femoral neck bone increased during the first year after landing, but the space flight induced decline in volumetric bone mineral density (g/ cm^3) was not significantly different one-year after return than immediately after spaceflight. These data suggest that radial bone growth was stimulated on return to Earth's gravitational field, but that the increase in bone mineral content was not sufficient to restore BMD to preflight levels. Furthermore, recovery of volumetric BMD in the trabecular bone compartment was not evident in ISS astronauts who were scanned at the hip by QCT within the first 2-4 years after return from space (Carpenter, 2010).

In contrast to DXA, QCT provides new data of the hip that expands the description of space-flight-induced changes and recovery after return from space. QCT revealed that after 12 months of re-ambulation on Earth, total hip bone volume increased at both the proximal femur (total hip) and femoral neck, whereas the vBMD was still decreased (ratio postflight vBMD /preflight vBMD <1) (Lang, 2006 a). This re-adaptation to Earth's 1-G field in middle-aged astronauts is similar to the expansion of bone's cross-sectional area observed in aging terrestrial populations and in individuals who have experienced weight loss (Riggs, 2004, Sukumar, 2011). Therefore, as part of a study extension, a fourth QCT hip scan was obtained 2-4 years after flight in 8 of the original 16 ISS crewmembers reported by Lang (2004). Figure 13 juxtaposes the different patterns of recovery in the hip and spine as assessed by DXA (aBMD) and QCT (tBMD = trabecular vBMD) scans. The aBMD in the lumbar spine tends to recover (L1-L4) after return, whereas trabecular vBMD ("Spine tBMD"), in QCT scans of L1 and L2, declines after the first year in all but one astronaut. The aBMD increased in the femoral neck in most individuals during the first year after return from space; however, one astronaut's femoral neck aBMD exceeded preflight measurements 4 years after return, whereas a reduction in trabecular vBMD of the femoral neck occurred over the same period (Carpenter, 2010). It was the opinion of some osteoporosis experts, convened in 2010 to assess the nature of these skeletal changes in long-duration astronauts, that failure to recover in QCT-measured vBMD of hip trabecular bone should be a trigger for further evaluation and possible intervention to prevent premature fragility

fractures (Orwoll, 2013). A pilot study to implement a QCT protocol for surveillance of this clinical trigger ("hip QCT") in ten astronauts was authorized in 2011 and will end in 2018.

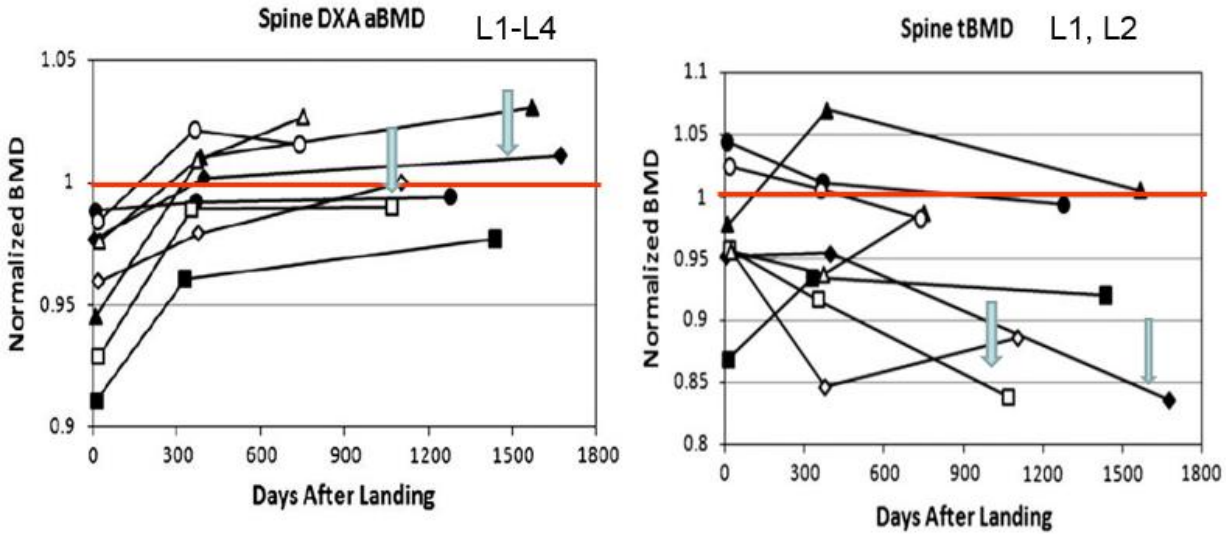

Figure 13a. Discordant patterns between skeletal changes to the lumbar spine, as monitored in identical crewmembers by DXA measurement of areal BMD (aBMD) of the vertebrae L1-L4 and by QCT detection of trabecular BMD of vertebrae L1, L2 (tBMD), is highlighted by arrows . L1-L4 = Areal BMD of Lumbar vertebrae 1 through Lumbar vertebrae 4. L1, L2 - Volumetric BMD of Lumbar vertebrae 1 and Lumbar vertebrae 2 are deemed sufficient to assess spaceflight effects. Normalized BMD = postflight measurement/postflight measurement where Normalized BMD = 1 denotes restoration to preflight value. Adapted from Carpenter 2010.

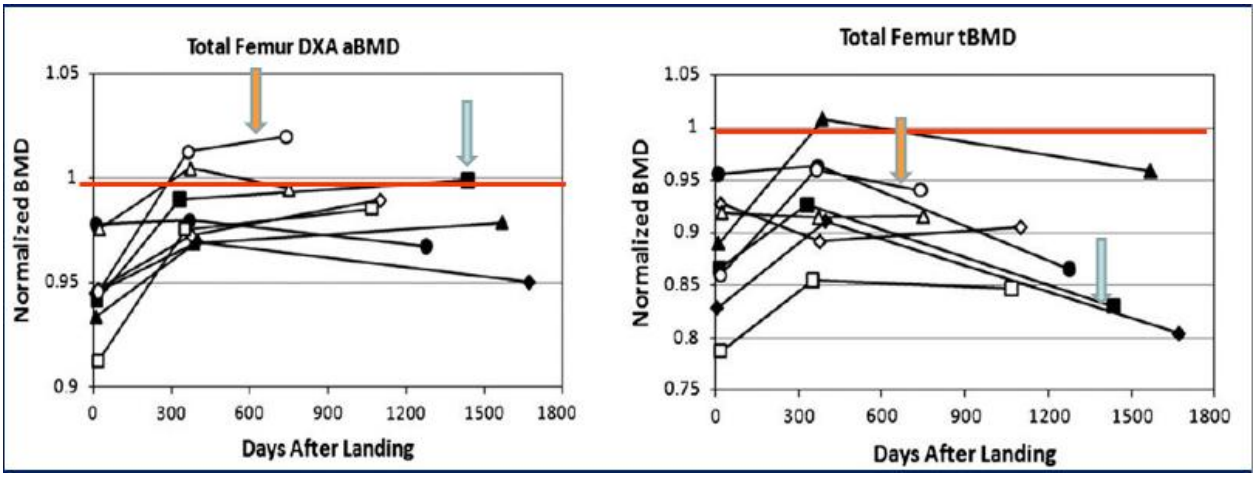

Figure 13b. Discordant pattern of skeletal changes to the total proximal femur (i.e., hip) as monitored in identical crewmembers by DXA measurement of areal BMD (aBMD) and QCT detection of trabecular BMD of total proximal femur (tBMD), is highlighted by arrows. Normalized BMD = postflight measurement/postflight measurement where Normalized BMD = 1 denotes restoration to preflight value. Adapted from Carpenter 2010.

2.3.1.3 Biochemistry Data

Biochemical analyses of bone turnover biomarkers in specimens collected post-mission indicate that the excretion of N-telopeptide (NTX) in urine (a biomarker for bone resorption) is restored to baseline when astronaut returns to Earth, and there is a delayed rebound (30 days after return from space) in serum levels of osteoblast-specific proteins (bone specific alkaline phosphatase and osteocalcin) that are biomarkers of bone formation (Smith, 2005) (Figure 14). This trend in biomarkers precedes the positive change in BMD and has also been observed in test subjects in the re-ambulatory period *following* skeletal unloading by prolonged bed rest (LeBlanc, 1990).

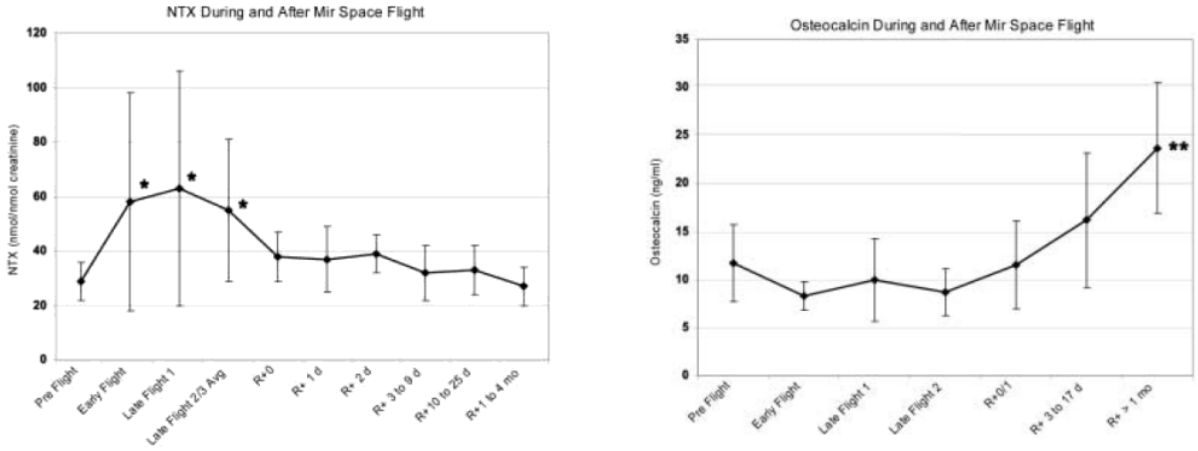

Figure 14 a, b. Bone turnover markers measured in specimens collected before, during, and after flight suggest that return to earth's 1-G environment reverses the increased excretion of bone resorption marker NTX (amino terminus of cross-linked collagen degradation product) and eventually stimulates expression of bone formation markers (osteoblast-specific osteocalcin) (Smith, 2005).

2.3.2 Comparison to Terrestrial Aging Population

The geometrical changes at the femoral neck of astronauts after return to Earth (i.e. increased cross-sectional area) is similar to the adaptive skeletal response to the cortical thinning and trabecular bone loss normally observed with age-related bone loss in the elderly (Mosekilde, 2000; Seeman, 2002). The geometrical changes in both of these cohorts suggest a compensatory physiological response of the skeleton to recover compressive and bending strength in the context of age-related bone loss. QCT analysis of bone geometry age- and sex-differences (Riggs, 2004) shows apposition of bone at the periosteal surface (outer surface) in response to thinning of the cortex by age-related increases in bone resorption at the endocortical surface (inner surface to bone marrow). Likewise, Lang reports radial increases in whole bone for the proximal femur and the femoral neck of astronauts after a 1-year postflight ambulation period in 1G (Lang, 2006 a; Carpenter, 2010). This comparison suggests that age-related changes in bone structure observed in the elderly are similar to the unexpected changes documented in *younger middle-aged* crewmembers after long-duration space flight. While the use of DXA measurement of aBMD and clinical risk factors (Kanis, 2001, 2007) may be adequate for evaluating the risk of fractures in a terrestrial population with primary osteoporosis (Zyssett, 2015), the ability to understand the effects of spaceflight fully -- and how this expanded definition could enhance

the management and care of astronaut skeletal health – may require transitioning research technologies to the clinical arena (Orwoll, 2013).

It may be possible to improve bone mass in individuals by modifying or correcting risk factors for bone loss. Individuals with age-related osteoporosis are supplemented with calcium and vitamin D to treat calcium malabsorption and its associated secondary hyperparathyroidism– an endocrine risk factor for bone loss (Dawson-Hughes, 1997; Boonen, 2006). Alternatively, anabolic therapy (e.g., Trademark Forteo) can provide the stimulus for osteoblastic bone formation (Holick, 2005; Riggs, 2005), and is recommended therapy for patients with severe osteoporosis (e.g.,BMD T-scores > -2.5 or presence of fragility fractures). Moreover, hormone replacement, or alternatively anti-resorptive bisphosphonate agents such alendronate and zoledronic acid, have been adopted to prevent or mitigate postmenopausal osteoporosis. Increased bone resorption accounts for menopause-induced bone loss (Cauley, 2003; Black, 2000). There are pharmaceutical agents currently in clinical trials, such as Denosumab (Amgen Prolia), anti-sclerostin monoclonal inhibitor (Amgen, Romosozumab) and cathepsin K inhibitors (Merck Odanacatib), available for further investigations in young healthy persons in ground-based analogs for space flight.

In general, osteoporosis that results from disuse-atrophy or from age-related changes (both type I and II) have different etiologies, i.e., different perturbations in the cellular-driven bone remodeling process that result in a net loss in bone mass. As previously described, increased activation of remodeling units during menopause results in a negative bone balance in the bone remodeling sites. When the initiation of bone remodeling is accelerated, the resorption of bone out-paces the formation of bone, resulting in a net under-filling of the resorption cavity. In general, bone *turnover* is assessed indirectly by analyzing biomarkers for bone resorption and bone formation, i.e. biochemical assays of circulating levels of peptides released specifically by bone-forming cells or of excreted by-products of resorbed bone. Assays of urine and blood specimens collected from astronauts before, during, and after space flight suggest that bone resorption is stimulated and bone formation is suppressed during space flight (Smith 2005, 2015). The prolonged deficiency of a mechanical stimulus appears to stimulate bone resorption, whereas bone formation is non-responsive or reduced (Forwood, 1995). Consistent with "Form follows Function", a paraphrase of Wolff's law, this interpretation suggests that the skeleton reduces its mass (and hence its biomechanical strength) as an adaptive response to reduced mechanical forces to the skeleton. Additionally, the site-specific skeletal adaptation to space flight—as seen with BMD losses specific to weight-bearing skeletal sites—underscores a local mediation of bone remodeling (paracrine vs. endocrine regulation), which would not be captured by a bone biopsy of the iliac crest alone. Moreover, skeletal adaptation to space flight might also involve the suppression of bone formation by an inhibitor of bone formation, sclerostin, which is produced by the SOST gene in osteocytes in response to reduced mechanical loading of bones. Increased sclerostin was detected in the sera of male test subjects exposed to prolonged bed rest and in the sera of ISS astronauts (Spatz, 2012; Smith, 2015).

DXA technology averages the measurement of bone mass in skeletal tissue throughout a projected 2-dimensional area of the imaged bone (cm^2 area). Hence, DXA cannot discern the location (i.e. cortical bone, cancellous bone) of bone loss and bone gain, and likewise cannot assess the distribution of bone mass in 3-dimension volume. Three-dimensional changes in whole bone geometry and size, and in trabecular microarchitecture, can influence whole bone

strength; hence, DXA is unable to measure key properties of bone that can be used to assess changes in bone's biomechanical integrity. Likewise, bone turnover markers are weakly correlated with changes in bone mass, and their ability to assess the fragile nature of bone is therefore very limited and indirect. Currently, bone turnover markers are not assessed in crewmembers unless the analysis is part of a research study. DXA measurement of aBMD is the only method currently used for monitoring change in skeletal health in astronauts; this limits HRP's understanding of the effects of space flight on overall skeletal integrity because a vital component of skeletal heath—osteoporosis skeletal fragility—is not assessed.

Lastly, there are multiple factors that may influence the differential rate of BMD loss in space and recovery after space flight. These factors that contribute to BMD loss are currently being assessed by epidemiologic analyses of surrogate measures including endocrine regulation, turnover rate, and radiation exposure. However, the limitation of this epidemiology study, and possibly all other similar studies evaluating skeletal bone changes, is the insufficient statistical power. Given the limited number of astronaut subjects, obtaining a level of evidence to substantiate a risk for early onset osteoporosis is not feasible. The lack of availability of evidence is compounded by (1) the large number of confounding variables (aside from microgravity), (2) the novel skeletal insult of space flight, and (3) the limited baseline skeletal knowledge for this target population (young, healthy, physically fit, predominantly male); hence, clinical experts have expressed a need for individualized fracture risk assessments (Orwoll, 2013).

IV.2.4 Perturbations in Bone Remodeling

2.4.1 Space flight Evidence

As previously mentioned, data from bone turnover markers suggests that the bone remodeling process is uncoupled in space. Normal bone remodeling, the skeleton's tissue renewal process, resorbs older or damage bone tissue, and once the bone is removed it is then replaced with newly formed tissue in the exact location. When bone remodeling is "uncoupled," the processes of bone resorption and bone formation are no longer linked, presumably due to disruption in the cellular signaling between bone cells; this disrupted mediation can lead to an unbalanced remodeling of bone and a potential net deficit in bone mass. Indirect biomarker measures of bone turnover for the entire skeleton suggest that bone resorption is increased and bone formation is unchanged or decreased. Early in the space program, biochemical assays of astronaut specimens collected in space flight detected a greater excretion of collagen degradation products relative to circulating proteins and peptides that are synthesized and released by osteoblasts during bone formation. Historical data document the following

1. Early assessments of reductions in bone mineral suggested the occurrence of bone atrophy and a risk to skeletal integrity (Vogel, 1976)
2. An increased excretion of hydroxyproline (a post-translationally modified amino acid specific to collagen) relative to pre-flight level in all 3 Skylab missions (Rambaut, 1979)
3. An increase (100-150%) in cross-linked collagen fragments at the amino terminus (NTX) during flight, determined in a retrospective analysis of in-flight urine specimens collected from Skylab crewmembers (Smith, 1998)

4. Increases in NTX during flight with minimal influence on serum osteocalcin (an osteoblast-specific protein) in Mir crewmembers (Smith, 2005)
5. Suppression of procollagen type I C-terminal peptide, bone-specific alkaline phosphatase, and osteocalcin (osteoblast-specific protein and peptide) concurrent with increased bone resorption markers (Caillot-Augusseau, 1998)

Recent reports have characterized the biochemical response to resistive exercise performed on the ARED and compared biochemical response to exercise performed on an interim resistive exercise device (iRED) (Smith, 2015). For resistive exercise to have a positive impact on bone mass, forces on bone need to approach 3 times body weight to overload the bone (Perusek G and Myers J, Exercise Countermeasure Project Bone Workshop Summary and After Action Report). The iRED was only capable of providing a maximum force of 300 pound of resistance, which is less than a typical resistive exercise regime an astronaut would perform before flight and might be sub-optimal for overloading bones and stimulating bone formation during space flight. Astronauts with access to the iRED only had increased levels of sclerostin, whereas a suppression of sclerostin was measured in astronauts using the ARED (both with and without bisphosphonate intake) (Smith, 2015). In addition, BMD declined from preflight values in crewmembers who used only the iRED exercise device (Lang, 2004; Smith, 2012), whereas the previously observed deficit in post-flight BMD (group means value) was attenuated in ARED users (Sibonga, 2016). Sclerostin is the protein product of the SOST gene that is expressed in osteocytes, the putative *gravity sensing* cells embedded in bone matrix. Sclerostin inhibits bone formation by interfering in Wnt signaling in osteoblasts. Increased expression of the SOST gene is associated with mechanical unloading, and increased sclerostin levels have been measured in patients with spinal cord injury (Gifre, 2015) and in stroke patients (Gaudio, 2010).

Collectively, these indirect, systemic assays of bone turnover suggest that remodeling is uncoupled with mechanical unloading, and as a consequence, the volumes of resorbed bone and formed bone within the remodeling unit are not balanced. Investigators continue to analyze biochemical trends with the goal of providing a biochemical profile of ISS astronauts.

2.4.2 Comparison to Aging Population

As previously described, bone loss during menopause is the result of rapid bone remodeling. Rapid remodeling can be characterized by activation frequency—an index of bone histomorphometry of iliac crest biopsies—that reflects a faster birth rate of new bone remodeling units (Recker, 2004) in perimenopausal and postmenopausal females compared to younger, premenopausal females. Bone biopsies, however, have not been performed in astronauts and, an increase in bone remodeling during space flight is implied by increases in bone resorption markers relative to preflight levels (Smith, 2005, 2015); increases in bone resorption are also observed with menopausal bone loss (Sornay-Rendu, 2005; Garnero, 1999). Moreover, the accelerated rate of bone turnover has been associated with a detriment to bone quality—specifically disruptions in bone microarchitecture—as observed with vertebral fractures in aging women after menopause (Kleerekoper, 1985).

IV.2.5 Related Risk Factors for Bone Loss

Bone loss can be a reflection of several processes, and thus the extensive variability observed with skeletal measures (e.g., BMD) is not unexpected. Several risk factors contribute to bone loss. Perturbations in endocrine levels observed on Earth could contribute to space flight-induced bone loss and may contribute to early onset osteoporosis.

2.5.1 Space flight Data

Evidence from short duration (< 90 days) space missions suggests that a negative calcium balance occurs in space and is due to a reduction in calcium intake and calcium absorption, and an increase in calcium excretion. Mineral metabolism studies that were conducted during the Skylab missions enabled Whedon and colleagues (1976a; 1976b; 1977; Smith, 1977) to characterize the negative calcium (and mineral) balance during space flight. Data were obtained from the total of 9 astronauts who flew on 3 separate Skylab missions lasting 28, 56, and 84 days (3 astronauts per mission). Despite the large variability in mean values, collectively the data suggest that the deconditioning of the skeleton increases with the duration of space flight (LeBlanc, 2007). Results also indicated a rapid and sustained elevation in urine calcium, a gradual increase in fecal calcium, and a negative calcium balance averaging – 5 g/month. These changes were accompanied by increased excretion of hydroxyproline and hydroxylysine (early biomarkers of bone resorption), gradual decreases in intestinal calcium absorption, minor increases in plasma calcium and phosphorus, and a delayed (>4 weeks) reduction in serum parathyroid hormone (PTH).

The Skylab data demonstrate that the negative calcium balance is likely due to bone atrophy (increased calcium excretion) and to calcium malabsorption (deceased calcium intake), and these results were corroborated with subsequent kinetic and metabolic studies on a 3 month joint NASA-Mir flight (Smith, 1999). Furthermore, the stimulation of bone resorption during space flight was re-affirmed with state-of-the-art assays for multiple cross-linked collagen biomarkers, conducted on specimens that were collected from Skylab crewmembers (Smith, 1998).

Whereas bone resorption appears to increase during space flight, levels of the calcium-regulating hormones parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D did not change in astronauts who participated in Mir missions (Smith, 1999; 2005). Likewise, a more recent report documents suppression of circulating levels of PTH (Smith, 2015).

These data suggest that increased demineralization of bone will mildly increase serum calcium and phosphorus levels, and lead to a reduction in the hormones responsible for preserving or increasing serum calcium (PTH and 1,25-dihydroxy vitamin D). These deficits will likely suppress intestinal absorption of calcium and re-absorption of calcium by the kidney, thereby contributing to the negative calcium balance seen with space flight.

2.5.2 Comparison to Terrestrial Aging Population

In the elderly population, calcium absorption is poor due to multiple factors such as an inadequate conversion of vitamin D by sunlight, reduced enzymatic conversion to 1,25-dihydroxyvitamin D, and a vitamin D receptor resistance. Renal insufficiency and nutritional deficiencies are both causal and contributing factors. Collectively, these co-morbidities result in hypocalcemia, and any resulting secondary hyperparathyroidism could induce bone loss in the elderly. Since a negative calcium balance has also been observed in space, this might indicate that astronauts incur risk factors for bone loss similar to those incurred with aging. However, it must be noted that the increased serum calcium resulting from stimulated bone resorption during space flight reduces intestinal calcium absorption in crewmembers, whereas calcium malabsorption in the elderly induces age associated bone loss. The poor calcium absorption in both of these cases does not suggest that treatment would be the same, as documented by Heer et al (1999).

In sum, data collection for the surveillance of bone health (i.e. longitudinal measures in crewmembers before, during, and after flight) is required to confirm that crewmembers are replete in vitamin D prior to launch and that they are sufficiently supplemented during flight to prevent decrements in bone health. Moreover, data collection, such as the upcoming Space Biochemistry Profile by JSC Nutritional Biochemistry lab, is required to monitor any endocrine perturbations in mineral metabolism during flight and/or to evaluate responses to countermeasures (Smith, 2012b).

Finally, the use of terrestrial-anti-resorptive osteoporosis therapies in young healthy astronauts (both men and women) is considered an "off-label" application for which there is minimal evidence to support this application. Osteoporosis experts (Bone Summit panel + 3 consultants) met in 2016 under the aegis of a Research & Clinical Advisory Panel (Bone RCAP); this is the third meeting of members to review astronaut biomedical data that include research data accumulated by QCT and the biochemical profile. The Bone RCAP stated that it will challenging, if not impossible, to predict which astronauts are more likely to lose BMD based on the data accumulated to date. Furthermore, because both flight and ground-based data support an osteoclast-driven net loss in bone mass, the most effective and operationally convenient intervention to mitigate bone loss and possible bone fragility would be to administer the bisphosphonate Zoledronic Acid [ZA] before flight. It is the opinion of members on the RCAP that ZA, which is given by infusion, should be offered to all astronauts (which includes commercial crewmembers) who are scheduled for space flight < 6 months, recommended to astronauts scheduled for space flights $\geq$ 6 months, and should be mandatory for any astronaut who participates in the 3 year Mars mission. Although uncertainty still exists, the concern is that irreversible changes to bone will occur if bone resorption is not abated during spaceflight.

IV.2.6 Decreased Bone Formation

2.6.1 Space flight Data

Space flight impairs the mineralization of bone. Histomorphometry of iliac crest bone biopsies that have been labeled with tetracycline (a bone fluorochrome), are the standard method

for evaluating mineralizing surfaces in skeletal tissue and for calculating rates of mineralization and formation. However iliac crest biopsies for bone histomorphometry have not been used to describe an impact of space flight on bone remodeling. As previously mentioned, the skeletal adaptation to space flight targets weight-bearing bones, suggesting that skeletal unloading affects the local regulation bone cells to demineralize bones. Hence, the non-systemic regulation reduces the clinical utility of iliac crest biopsies to reflect remodeling at other skeletal sites. Histomorphometry data, however, have been obtained from bone biopsies of non-human primates that were administered tetracycline prior to launch into space (Zerath, 1996; 2002). Compared to biopsies obtained before flight and from controls on the ground, there was a significantly reduced area of bone (with a tendency for thinner trabeculae) and reduced percentage of mineralizing surfaces in biopsies obtained after landing. The reduction in bone was accompanied by a reduction in bone mineral content during flight.

2.6.2 Ground-based Data

Ground-based analogs of space (Spector, 2009) can better accommodate the use of invasive analytical methods, and experiments evaluating mechanical unloading of the skeleton can be carefully controlled. The following reports from space flight analogs corroborate and enhance the limited space flight opportunities.

1. Immobilization or mechanical unloading by prolonged bed rest down-modulates calcium-regulating hormones (Stewart, 1982; Arnaud, 1992; LeBlanc, 1995).
2. Mechanical unloading by prolonged bed rest uncouples remodeling, as reflected by bone turnover markers (Lueken, 1993; LeBlanc, 2002; Smith, 2003; Shackelford, 2004).
3. Mechanical unloading of skeleton uncouples osteoclastic and osteoblastic mediation of bone remodeling, as determined in bone biopsies (Minaire 1974; Vico, 1987; Zerwekh, 1998).
4. Mechanical unloading by 120 days of bed rest (Thomsen, 2006) and during >two years following spinal cord injury (Modlesky, 2004) deteriorates connectivity of trabecular microarchitecture.
5. Mechanical unloading by spinal cord injury induce profound skeletal changes (below the spinal lesion) (Vestergaard, 1998; Chantraine, 1986;Lazo, 2001) that can be used to verify novel tests and skeletal parameters to inform fracture risk assessments in astronauts (Eser, 2004).
6. Mechanical unloading by 90 days of bed rest increases postural instability in test subjects which may increase the risk for falling and possible overloading of bones (Muir, 2011).
7. Performance of resistive exercise under artificial gravity (e.g., induced by lower-body negative pressure or short-arm centrifuge) may have concurrent benefits to cardiovascular and musculoskeletal systems (Hargens, 2013).
8. Skeletal unloading in non-human primates immobilized in a space flight analog impairs mineralization, accelerates bone resorption, and reduces bending strength (Young, 1983; Mechanic, 1986; Young, 1986).
9. A large animal ovine model can successfully simulate the tissue effect of skeletal unloading to bone remodeling, as observed in rodent models with hind limb elevation, and may better facilitate studies evaluating effects on Haversian remodeling in cortical bone (Gadomski, 2014).

The collective histomorphometric data from humans and non-human primates indicate (1) that skeletal unloading uncouples bone remodeling, (2) that the level of bone resorption exceeds the extent of bone formation, and (3) that mineralization is impaired.

Moreover, ground-based investigations enable a more detailed assessment of in-flight exercise to preserve bone health. While weight-bearing exercises performed on the ARED have informed the required magnitude of resistive forces to help preserve bone mass, the optimal exercise prescription to prevent the physiological deconditioning, and possible declines in human performance, remains undefined. A ground-based study used prolonged bed rest as an analog for spaceflight to test the concept that a bolus of exercise in ~ 1 hour could substitute for 23 hours of skeletal unloading in space (Cavanagh, 2016). An individualized prescription of fully-loaded treadmill locomotion was derived from a summation of daily load stimulus (DLS) (Cavanagh, 2016). The exercise only attenuated the decline in muscle force production and the loss muscle volume loss in the quadriceps and calf muscles; bone loss was only partially prevented in the cortical bone shell of the hip suggesting that the DLS (Cavanagh, 2016). Collectively, an exercise prescription based upon the DLS may not be sufficient to prevent musculoskeletal deconditioning in astronauts during spaceflight (Cavanagh, 2016).

Moreover, a novel analysis of QCT scans enabled investigators to capture the effect of mechanically loaded exercise on the spatial heterogeneity of the hip (Zhao, 2010; Lang, 2014) although the verification of this analysis in a spaceflight analog was not possible due to scheduling constraints in the JSC Flight Analog Project.

2.6.3 Comparison to Aging Population

Involutional bone loss in the elderly (type 2 primary osteoporosis) is associated with suppressed bone formation (Riggs, 1986). Resorption lacunae may be of normal depth, but osteoblasts have reduced capability to sufficiently replace resorbed bone (Lips, 1978). More recently, age-related differences in males characterized by iliac crest biopsies, reveal reductions in bone formation in a cohort of pristine skeletal health, which are due to a reduction in matrix production and mineralizing activity of osteoblasts (Clarke, 1996, Figure 2-15).

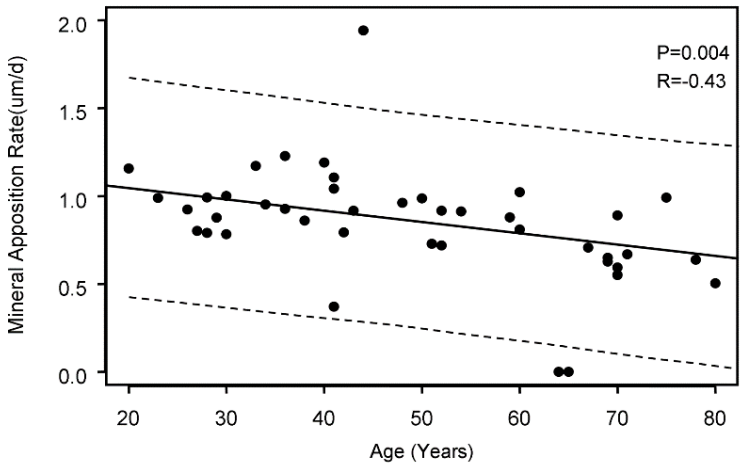

Figure 15. Significant reduction in mineral apposition rate in iliac crest biopsies of aging men substantiates an age-related decline in osteoblast activity. (Clarke, unpublished data).

One possible mechanism for reduced bone formation that occurs in space and with aging has been attributed to the osteocyte. The osteocyte is the putative gravity-sensing cell that could mediate the skeletal response to mechanical loading or unloading by either receptor activation of nuclear factor-kappa beta ligand (RANKL), which is an activator of osteoclast formation, maturation and survival; or by induction of sclerostin, which is a product of the SOST gene and is capable of inhibiting osteoblast-driven bone formation by modulating osteoblast apoptosis (Robling, 2008). ELISA [enzyme-linked immune sorbent assay] can be used to measure circulating levels of sclerostin in humans under conditions of skeletal unloading or disuse (Gaudio, 2010; Spatz, 2012). Healthy male test subjects (31±3 years old) who were subjected to prolonged bed rest (28, 60, or 90 days) had elevated levels of sclerostin than before bed rest (albeit non-significant at 90 days) (Spatz, 2012). Sclerostin levels were associated with reductions in BMD and with elevated biomarkers for bone resorption, which consistently observed in bed rest subjects (Spector, 2009). Biomarkers for bone formation remained unchanged relative to pre-bed rest levels, supporting a mechanism for the uncoupling of bone formation from bone resorption during mechanical unloading. Finally, the beneficial influence of lower body negative pressure to promote blood flow in the lower limbs of the body suggests the contribution of cephalad shifts to the atrophy in the weight-bearing skeletal sites (Siamwala, 2015; Macias, 2012; Mateus, 2012; Smith, 2003).

A comparison between space-induced bone atrophy and age-related osteoporosis indicates that reduced osteoblast activity or number are associated with the skeletal changes that occur in space and with aging, and may be related to an increased production of an osteoblast inhibitor that occurs during skeletal disuse. Histomorphometry of iliac crest biopsies from *healthy* individuals substantiates that the leading contributor to age-related bone loss in males is the reduction in bone formation, whereas an increase in bone turnover more likely influences bone loss in the aging female during menopause (Recker, 1988; Clarke, 1996). Post-menopausal women with spinal cord injury had 34% greater index of trabecular separation than pre-menopausal women with spinal cord injury, suggesting interaction between mechanical unloading caused by paralysis and estrogen insufficiency (Slade, 2005). Moreover, the systemic, tissue, and cellular responses to mechanical unloading resemble the combined response of skeletal cells and tissue to aging, regardless of sex, i.e. increased resorption and suppressed formation. The effects of menopause may accentuate the effect of mechanical unloading on bone microarchitecture. However, depressed cellular function and number during space flight, determined by bone histomorphometry, have not been confirmed in astronauts.

V. COMPUTER-BASED MODELING AND SIMULATION

There is no ethical method of accurately testing the mechanical strength of the skeleton in the human. Finite Element Models (Finite Element [FE] modeling [FEM] or Finite Element Analysis [FEA]) is a computational tool used by engineers to assess the biomechanical integrity of complex structures, such as aircraft and automobiles, which has in vivo applications to biological systems (Crawford, 2003; Keyak, 2005). FE modeling has been used to estimate whole bone strength using computer-generated models of 3-dimensional images and densitometry data obtained from skeletal scans by Quantitative Computed Tomography [QCT] (Crawford, 2003; Keyak, 2005). Moreover while computer modeling has also being investigated as a sophisticated tool for predicting changes in volumetric BMD of the hip (Pennline, 2014), verification of the

tool is not yet fully accomplished because limited QCT data is available from ground-based (bed rest subjects) and spaceflights (astronauts).

V.1 Space flight Data

Finite Element Modeling was conducted on QCT hip scans of 11 ISS crewmembers to evaluate space flight effects on sub-regional cortical and trabecular compartments of the hip (Lang, 2004; Keyak, 2009). The FE modeling software uses 3-D images of QCT hip scans to determine force-to-failure (kN or N) for mechanical loading of the femoral neck at 2 specific orientations and was verified against mechanical strength testing in cadaver specimens (Figure 16a, b): the posterior lateral direction (Figure 16a, associated with falls backward and to the side) and the axial direction (Figure 16 b, associated with single-legged stance loading) (Keyak, 2005). From herein, these estimations of "bone strength" will be referred to as FE Fall Load and FE Stance Load. The analysis of FE models, that were generated from crewmember QCT hip scans performed preflight and postflight, determined a significant reduction, during spaceflight, in the both FE Fall Load and FE Stance Load after a 6 month mission (group mean value, n=11).

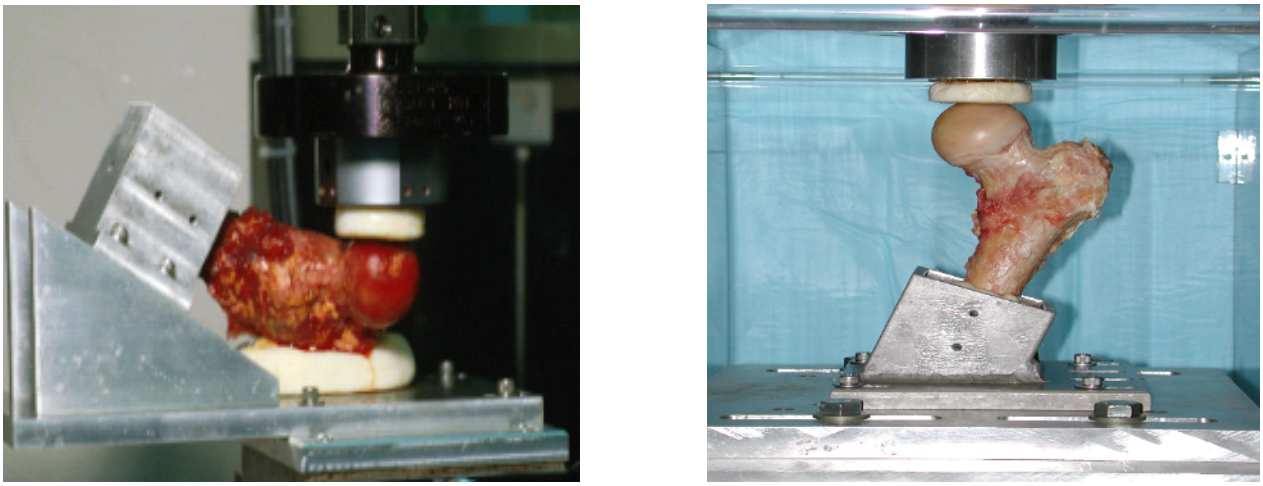

Figure 16 a, b. Finite element analysis of models generated from QCT data of ex vivo hip bone specimens was used to estimate mechanical strength of hip for two loading conditions: Stance (right image) and fall loads (left image) (Keyak, 2007). The estimations of hip strength were validated in a 2nd set of cadaver specimen with mechanical strength testing (loaded to failure)

Of the 11 crewmembers evaluated (Keyak, 2009), 2 crewmembers lost up to 24-30% hip strength for either FE Stance or FE Fall loads (Figure 17). When loss of strength was averaged on a monthly basis, there was an approximately 2-fold reduction in the median hip strength (Stance loads 2.2%,; Fall loads 1.9%) for each 1- fold reduction in mean aBMD (1.2% femoral neck; 1.6% trochanter) (LeBlanc, 2000) Table 7. Similar trends and magnitude differences for FE strength and by aBMD were observed in the proximal femur (hip) of patients with acute spinal cord injury (Edwards, 2014).

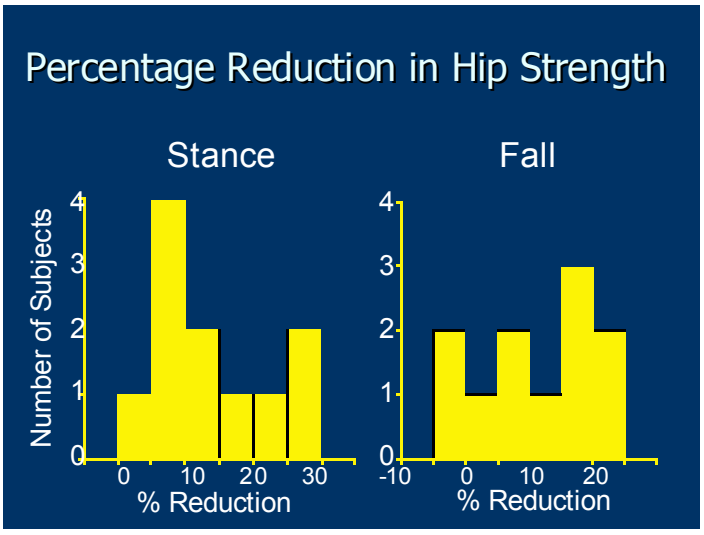

Figure 17. Number of crew members per quantified reductions in hip strength. Up to two long-duration crew members experience 20-30% reduction in hip strength for both loading scenarios (Keyak, 2007).

The FE estimations of hip strength were obtained from 5 crewmember subjects 1 year after return from space, providing complete modeling at 3 time points (preflight, postflight, and 1 year after return). There is a trend towards recovery of hip strength (4/5 show minimal recovery in Fall Load, 4/5 show strong recovery in Stance Load) (Lang, 2006 b). However, QCT does not have the resolution for detecting disruptions in trabecular microarchitecture (a hallmark of osteoporosis). Consequently, with this remaining uncertainty, there is the possibility that hip strength and actual fracture risk may be underestimated.

Loading Condition	**Mean (SD) Preflight**	**Mean (SD) Postflight**	***p***
Stance	13,200 N (2300 N)	11,200 N (2400 N)	<0.001
fall	2,580 N (560 N)	2,280 N (590 N)	0.003

Table 7. Significant reduction in failure loads of hip after ~6 month space flight mission for n= crew members (Keyak, 2007).

V.2 Comparison to Terrestrial Aging Population

The same FE modeling protocol used in astronaut QCT scans was also applied in a cross-sectional comparison of hip strength in young and elderly women (N=128 postmenopausal [70 – 80 yr] females versus n=30 pre-menopausal [35-45 yr] females). The mean percentage reductions observed with aging in a cross-sectional study of females was 7% for stance loads and 24% for fall loads (Table 8). The median percentage reduction in hip strength for the 11 crewmembers serving on 6 month flight missions was 13.1% for stance loads and 13.7% for fall loads.

Loading condition	Lifetime loss in ageing female, mean	Loss after ~6 mo in space, median (range)
Stance	6.9%	13% (4 to 30%)
fall	24.4%	14% (0 to 23%)

Table 8. Perspectives on hip strength loss (Keyak, 2007).

This comparison indicates that the reduction in hip strength after 6 months of weightlessness is comparable (~50%) to lifetime reduction in hip strength (for fall loads) in aging females, though cross-sectional (vs. longitudinal) assessments limit understanding of temporal effects on the skeleton (Melton, 2000). The hip strength of some crewmembers appears even lower for the stance loads when compared to elderly females. The hip strength for stance load is greater than for fall load (Table 8) because the superior portion of the hip (vs. the inferior) adapts to axial loading with standing and walking. In contrast, the hip strength for fall load represents a site within the bone that has fewer opportunities to adapt to falling.

A recent study of FE hip strength (both FE loads) and areal BMD from all atronauts with QCT data (n=31) assessed how these two indices of bone strength captured changes during space flight (Lang, 2004; LeBlanc, 2013, 2017). The regression between percent change in non-linear fall loads vs. % change in DXA total hip aBMD was R = 0.71, R^2=0.51: the regression between percent change in non-linear stance loads vs. % change in DXA total hip aBMD was R = 0.75, R^2=0.57. Notably, regressions do not indicate the accuracy of one method over another. However, one study compares the accuracy of 3 mathematical algorithms for calculating bone strength that were developed by analyzing ex vivo bone specimens by DXA, QCT, and FE modeling of QCT data. The derived algorithms were then tested on a second set of ex-vivo bone specimens to verify the predicted strengths with regression to force-to-failure testing (Cody, 1999). The results indicate that QCT (R^2=.66) outperforms DXA (R^2=.57) to estimate the mechanical strength of these bones, but that FE modeling of QCT data (R^2=.84) is best for predicting hip strength (Cody, 1999). This assertion has been further substantiated by a meta-analysis conducted for a position development by the International Society for Clinical Densitometry (Zysset, 2015). In addition, it is critical to recognize that the FE modeling approach integrates mutliple attributes of bone (3D-BMD, geometry, material property, loading) into estimates of bone strength, whereas hip aBMD represents a single property serving as a *surrogate* for bone strength.

V.3 Relevant Investigations in Animal Models

Animal studies that are most relevant to HRP Evidence Report are those investigations that generate data, assess comparative effects and provide fundamental knowledge that cannot be acquired easily in astronauts due to issues related to ethics, time involvement, invasive testing and statistical power. While some of the acquired knowledge may not be considered "essential" for or to directly translatable to the clinical mitigation of human risks, the insight gained (much of which is acquired through invasive testing) could enhance the interpretation of evidence acquired by more clinically useful, but indirect and subjective human testing. Recent knowledge gained from ground-based animal models have involved:

- *In situ* assessments via histology and histomorphometry (Shirazi-Fard, 2015)

- Evaluation of genetic and epigenetic factors that modulate bone loss with disuse and recovery with r-eambulation (Judex, 2009; 2013)
- Early testing and verification of signaling mechanisms of potential countermeasures, e.g., vibration (Judex, 2010)
- Experimental simulation of mission operations such as multiple exposures to skeletal unloading, the combined effects of radiation- and unloading-induced bone loss and the influence of partial gravity (Shirazi-Fard, 2013a, b; Gupta, 2013; Macias, 2016) and
- Effect of ionizing radiation on bone, muscles, vasodilation and osteogenic potential after exposure (Bandstra, 2009; Shirazi-Fard, 2015; Prisby, 2016).

VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

The aforementioned biomedical data from astronauts were presented to a Research & Clinical Advisory Panel (RCA) in 2010. This 2010 NASA Bone Summit panel was charged with reviewing the accumulated biomedical data from astronauts who participated in long-duration missions and assess if, in their expert opinions, there is a need for an intervention to mitigate the risk for osteoporosis incurred by space flight. Because of the panel's expertise in bone loss risk factors, aging studies and clinical trials of osteoporosis therapies, the panel was also requested to comment on data acquired to-date from flight and ground-based studies that are still in progress. A Bone RCAP convened in 2013 and 2016 to conduct similar reviews of accumulated data to-date and for members to express their opinions based on updated knowledge in terrestrial medicine (See Appendix, Executive Summaries of Bone RCAP meetings).

VI.1 Space flight Data from Flight Investigations of Countermeasures

As previously mentioned, the ARED became available for use on the ISS in 2009 and this device provided higher fidelity resistive exercise than previous exercise devices. The ARED exercise hardware provides a resistance up to 600 pound force (lbf) for weight-bearing exercise that more closely induces the physiological impact of resistive exercise performed with free weights (concentric to eccentric loading at 90%). The previously reported declines in average aBMD for astronaut's skeletal regions have been reduced by ARED use or bisphosphonates supplements (Figure 18).

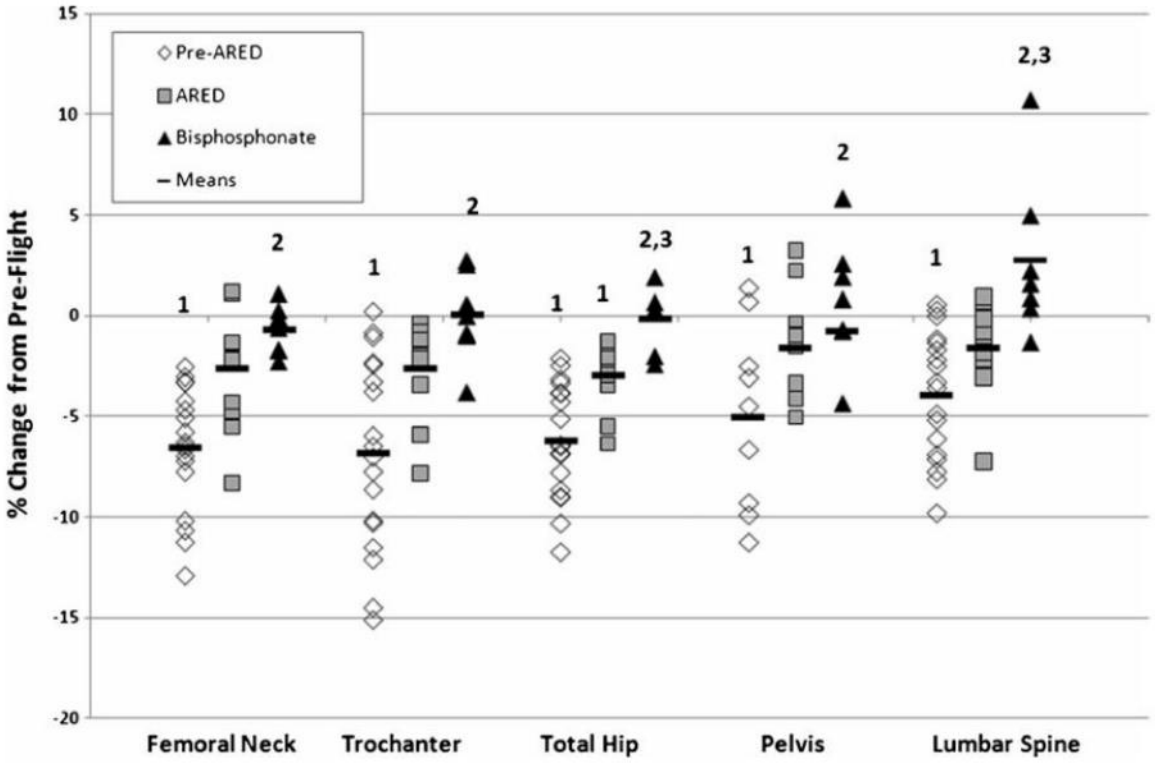

Figure 18. Effect of Bisphosphonate alendronate + ARED exercise (LeBlanc, 2013) on Total change in aBMD, as a percentage of preflight measurement, over entire mission served on Mir (Pre-ARED only) and ISS. Significant changes in group means aBMD, from preflight, are detected in both Mir and ISS crewmembers although the change in crewmembers with access to ARED was significantly different from crewmembers before ARED was available (Pre-ARED). Likewise, the combination of ARED exercise and bisphosphonates was significantly different from crewmembers who exercised on ARED with no bisphosphonate intake (data not shown, LeBlanc, 2017). However, the relative contribute of exercise from bisphosphonates cannot be discerned with aBMD measurements only.

Figure 18 shows the average decline in percentage of preflight aBMD (black bar) over the entire mission duration superimposed on a scatterplot of data from crewmembers participating in the bisphosphonate supplemental medical objective flight experiment. The scatterplot displays data from 3 groups of ISS crewmembers: Pre-ARED represents18 crewmembers (cosmonauts and astronauts who participated a previous fight study (Lang 2004, 2006) and only had access to the iRED for resistive exercise; the data denoted as ARED represent 9 crewmembers with access to the ARED (dark circles); the final column to the right presents data from 7 crewmembers who performed resistive exercise on the ARED while participating in a flight study to test an oral bisphosphonate as countermeasure for bone loss (LeBlanc, 2017).

The aBMD data by DXA, in response to ARED exercise, are encouraging because the skeletal benefit of having higher bone mass over lower bone mass is incontrovertible. However, DXA technology is limited by its inability to delineate the separate skeletal effects of the two interventions (i.e., resistive exercise and a pharmaceutical agent); the experimental design did not include astronauts treated with bisphosphonates alone. Each of these interventions might have a distinct influence the sub-regions of the hip bone (cortical vs. trabecular bone) and, as a result, differentially contribute to the strength of the whole hip bone (Keaveny, 2008). For example, the PATH study (Keaveny, 2008) demonstrated that the combined effect of the

bisphosphonate alendronate (an antiresorptive) with intermittant parathyroid hormone (PTH) (an anabolic) in postmenopausal females vs. untreated control was not significant by DXA aBMD. However, QCT was able to reveal that the beneficial effect of intermittant PTH was in its stimulation of bone formationin the trabecular vBMD. Because DXA measurement of aBMD (g/cm^2) integrates the bone mass measurements of cortical and trabecular sub-regions into one averaged 2-dimensional measurement the contribution of the highly dense cortical bone masks and overwhelms the measurement of the trabecular bone.

QCT bone parameters such as percent cortical bone volume, trabecular vBMD and minimal cross-sectional area, are additional predictors of hip (femoral neck) fractures, independent of predictions from DXA measurements (Black, 2008). Consequently, the clinical experts convened in 2010 for a Bone Summit asserted that an informed clinical opinion from the panelists could not be provided until QCT-derived parameters are obtained from astronauts who use ARED but do not take alendronate (Orwoll, 2013). In 2016, a Bone RCAP evaluated the DXA, QCT, and FE hip strength data from the Bisphosphonate Flight Study. The Bone RCAP considered the anti-resorptive effect of alendronate in this study to be compelling and, *in the opinion* of the Bone RCAP experts, a bisphosphonate, i.e. Zoledronic Acid, is warranted for crewmembers who participate in space flight missions. See the Appendix for Executive Summary 2016.

VI.2 Level 4 Evidence Expert Opinion: Clinical Interpretation of NASA Biomedical Data for the Osteoporosis Risk

As previously mentioned, the Bone Summit RCAP that convened in Houston in 2010 was charged with reviewing the biomedical data from astronauts who participated in long-duration missions and providing opinions for surveying and managing bone health in the context of NASA's constraints. To paraphrase, what does NASA need to do in the short-term "to manage an occupational risk for fractures that may occur later in life?" Given that no astronaut has returned from a long-duration space flight with a hip or lumbar spine T-score less than -2.5 (Figure 9), the panel was asked how NASA should interpret and utilize these medical test results, along with biomedical research data, to assess fracture risk in astronauts.

The Bone Summit RCAP is comprised of recognized policy-makers and position developers in the osteoporosis field, principal investigators of cohort studies of bone health in aging terrestrial populations, consultants in clinical trials and experts in bone loss risk factors. This RCAP recognized that a full, meaningful characterization of the skeletal response to space flight in astronauts might not ever be achieved, i.e. it is unlikely that NASA will reach the level of clinical evidence required by terrestrial standards to substantiate a risk or the requirement for intervention. In other words, the relationship between space flight-induced changes in bone mineral density, bone quality, and fracture outcome would not be established (NIH, 2001) to formulate clinical practice guidelines for astronauts flying on the exploration class missions beyond the ISS.

In particular, the panel asserted that evaluation of trends in astronaut data is limited by the type of bone measures, the delayed accumulation of data, and the small number of astronauts. Moreover, the uncertainties associated with the limited bone parameters measured in astronauts

(i.e. aBMD and biochemical markers), suggest that more sensitive and innovative approaches may be required for longer-term surveillance. On the basis of emerging evidence from innovative research to predict fracture in terrestrial populations (Orwoll, 2009; Keaveny, 2010; Keyak, 2011), the Bone Summit Panel recommended measuring bone structure and separate bone compartments in ISS astronauts, using QCT for FEMs, and estimating hip strength to increase the understanding of space flight effects and possibly to inform operational and clinical decision-making, especially for missions more than 180 days.

2.1 Bone RCAP Overall Assessment of the Risk and its Management

The Bone Summit RCAP offered the following interpretations and comments, which formed the basis of HRP risk mitigation Gaps (Section VII). Excerpts of the RCAP's comments are provided below, although the complete interpretations and recommendations from the Bone Summit Panel (Sibonga, 2016) have been also published in a peer-reviewed journal (Orwoll, 2013).

a. "In the panel's opinion, interventions to mitigate bone loss during space flight are advisable for long-duration astronauts, in order to minimize risk for adverse skeletal effects later in life. However, because the long-term adaptation of bone to space has only been evaluated in a small number of astronauts, the panel considers the available data insufficient to confidently recommend a specific therapeutic course of action. Additional well-designed studies are warranted."
b. "The complexities of space flight-induced bone loss in a small understudied population raise the question of whether current assessments of skeletal health in astronauts are sufficient."
c. "Regardless of the technique used, it is difficult to investigate the effects of space on bone, or of the different interventions for bone loss in the flight environment, when the number of long-duration astronauts is so small."
d. "It is recognized that a recommendation based on an established relationship between QCT-based measures and fracture risk is a standard that is impossible to meet considering the limited data available on astronauts. Nevertheless, the uncertainties associated with the assessment of bone character with aBMD in astronauts suggest that more sensitive and innovative approaches may be required for longer-term surveillance."
e. "…group trends in biochemical markers of bone turnover from U.S. crewmembers aboard both the ISS and Russian Mir spacecraft (Smith, 2005)…. suggesting that an uncoupling of bone resorption and formation occurs. The increase in bone resorption, without an increase in bone formation, could be expected to yield net loss of bone mass."
f. "As surveillance data accumulate for the astronaut population, recommendations for future extended missions beyond low Earth orbit should be formulated or modified."

2.2 RCAP Interpretation of DXA as a Risk Surveillance Technology

a. "The NASA Space Flight Human System Standards are criteria to establish ranges of crew health required to optimize health and performance during space flight missions (*Figure 9, in this Evidence Book)*. Consequently, these medical standards -- for selecting applicants for astronaut candidacy, for certifying an astronaut for a space flight mission or for disqualifying an astronaut from a second space flight mission – could be used to protect those astronauts who are at greater risk for losing bone strength during space flight that would put them at increased fracture risk with subsequent aging. The current standards are based upon aBMD by DXA, which may not capture all parameters of bone strength and fracture risk."
b. "…there is considerable heterogeneity in the extent to which aBMD is regained after flight …. Notably, DXA measurement of aBMD is often the only index considered when evaluating the efficacy of in-flight bone loss countermeasures and the return of bone health following flight. Overall, there is concern that DXA may underestimate skeletal risks due to space flight and re-ambulation on Earth,"
c. "… DXA, for example, cannot distinguish cortical restructuring (i.e., modeling) that has occurred as the result of space flight, that could occur with exercise loading of bones during space flight, or could occur after return to Earth's gravity (Lang, 2006). An increase in cortical bone will likely overwhelm the aBMD measure and mask quantitatively less impressive but biomechanically important effects in trabecular bone."

2.3 RCAP Rationale for QCT as Surveillance Technology for Bone Health

a. "QCT can provide additional information at the hip regarding space flight-induced changes, and recovery after return."
b. "…8 of the original 16 ISS crewmembers …displays different patterns of recovery (*Figure 8, in this Evidence Book)* in the hip and spine as assessed by DXA and QCT scans." (Carpenter, 2010; Orwoll, 2013)
c. "…the impact of space-induced skeletal changes on hip strength will remain an open issue for NASA until structural indices of bone in long-duration astronauts, such as those acquired with QCT, can be serially evaluated."
d. "Although the exact contribution of trabecular bone loss or structural change on hip strength requires further definition, the absence of recovery-to-baseline measurements in trabecular bone indicates irreversible changes in strength have probably occurred. Therefore, it could be clinically meaningful to implement QCT hip scans to assess the efficacy of new in-flight countermeasures and for surveillance postflight, where an absence of recovery could be a trigger to review bone health risk factors and/or to consider intervention to prevent expected age-related bone loss."
e. "…the panel recommends that all long-duration astronauts be evaluated for space flight-induced changes in separate compartments of the hip (total, femoral neck, and trochanter) by conducting preflight and postflight QCT-based measures. … that QCT measures be incorporated in a surveillance program and the evaluation

of astronaut eligibility and that efforts to better understand the appropriate role of QCT measures should be ongoing."

2.4 RCAP Recommendation on Other Technologies and FEM for Risk Surveillance

a. "The heterogeneous changes in the spine with aging, however, are problematic…new technologies and analyses should be explored in research studies…."
b. "The specific changes to bone microarchitecture (e.g., trabecular thickness, trabecular separation, connectivity, etc.) and their impact on strength and fracture risk will require further research since QCT does not detect trabecular microarchitectural changes."
c. "These data do not indicate whether DXA or FEM is superior in predicting bone health but do suggest that FEM may capture changes in bone that DXA does not (Keyak, 2009)."
d. "Computation of QCT-FEM strength can complement the existing medical assessment tests (DXA and bone turnover markers) and the more conventional QCT structural indices. As mentioned above, declines in bone strength, estimated by FEM, are evident after space flight, in spite of the pristine medical history and extreme physical fitness of the typical astronaut before space flight (Keyak, 2009). Emerging data indicate that FEM estimates of hip strength may be related to fracture risk (Orwoll, 2009; Keaveny, 2010; Keyak, 2011), especially in combination with aBMD."
e. "The use of multiple determinants of bone strength (Keyak, 2005) by FEM, in conjunction with the single aBMD surrogate for bone strength, may enhance the assessment of fracture probability in each astronaut for individualized clinical decisions. Finally, data from QCT and FEM strength modeling can be used to optimize a probabilistic fracture model, developed by NASA, to calculate applied loads to bones and fracture probability (Nelson, 2009)."

Investigators and clinical experts in osteoporosis, bone loss risk factors and bone densitometry have convened in Houston (2010, 2013, 2016) to review accumulated biomedical data from astronauts who participated in long-duration missions (see addenda for Executive Summaries of most recent reviews, i.e., Level 4 Evidence). In 2016, after three occasions of reviewing data, the experts on this panel asserted that, even in the absence of osteoporotic fractures in astronauts, there is enough evidence to recommend a countermeasure to mitigate the risk of premature fragility fractures during the long-term health of astronauts. Based upon expert opinion, the bisphosphonate, zoledronic acid, should be included in the arsenal of in-flight countermeasures to prevent bone loss. This assertion is not only based upon the review of astronaut data by panel experts, but upon their assessments and knowledge of:

a. the data-driven therapies for the prevention of osteoclast-driven bone loss in terrestrial medicine,
b. the inability to predict bone loss in the small number of astronaut subjects (even with access to ARED),

c. the operational safety and convenience of ground-based infusion of zoledronic acid 3-6 months prior to launch,
d. the long-term potency of zoledronic acid (up to 5 years) precluding repeat infusion during a mission and
e. the risk of irreversible changes to trabecular bone microarchitecture due to accelerated rate of bone loss.

VII. GAPS

Based on the opinions expressed by osteoporosis experts who participated in the 2010 Bone Summit, a Bone Research program (tasks to address critical issues for discerning if astronauts are at risk for early onset osteoporosis) was formulated by the JSC Bone Discipline with the following Gaps and the associated HRP deliverable categories (in **CAPS** HRP Unique Processes, Criteria, and Guidelines). This revision to the original GAPs of the emerging Human Research Roadmap (2008) prioritizes research and knowledge considered to be essential for the mitigation of early onset osteoporosis:

Osteo 1: A new acceptable bone health standard using an improved surrogate for bone strength needs to be defined for the flight environment.
POLICY ON STANDARDS
Osteo 2: What is the incidence & prevalence of early onset osteoporosis of fragility fractures due to exposure to space flight?
KNOWLEDGE GAP - EVIDENCE
Osteo 3: We need a validated, clinically-relevant method for assessing the effect of space flight on osteoporosis or fracture risk in LD astronauts.
KNOWLEDGE GAP – ENABLING TECHNOLOGY
Osteo 4: We don't know the contribution of each risk factor on bone loss and recovery of bone strength and which factors are the best targets for countermeasure application.
KNOWLEDGE GAP - DATA
Osteo 5: We need an in-flight capability to monitor bone turnover and bone mass changes during space flight.
MITIGATION GAP – DETECTION
Osteo 6: How do skeletal changes due to space flight modify the terrestrial risk of osteoporotic fractures?
MITIGATION GAP – SURVEILLANCE
Osteo 7: We need to identify options for mitigating early onset osteoporosis before, during and after space flight.
MITIGATION GAP – PREVENTION & TREATMENT

VIII. CONCLUSION

Substantiating whether space flight increases the risk for premature osteoporosis in astronauts who participate in long-duration missions ultimately centers on determining if space-flight-induced skeletal changes are irreversible after return to Earth. If space-flight-induced bone loss is not restored and decrements in whole bone strength persist into the post-flight period, then

crewmembers may experience the combined effects of space and of aging on the long-term health of the skeleton, and could be predisposed to an earlier diagnosis of osteoporosis or incidence of fragility fractures. An analogy is seen with the skeletal effects of menopause predisposing females to a premature incidence of fragility fractures compared to males.

Managing HRP health risks requires an understanding of the current evidence base for musculoskeletal de-conditioning in space and recognizing the gaps in or limitations of the accumulated knowledge. However, unlike aging populations on Earth, the subject pool of long-duration astronauts (which is predominantly male) is very low in number. Many open issues exist because astronauts compose a younger-aged, physically-fit cohort that is not typically studied for osteoporosis here on Earth (minimal baseline knowledge) and is exposed to a rare skeletal insult (minimal flight knowledge). Given NASA's constraints in data acquisition and the widely-recognized limitations of clinical testing, the interpretations and opinions (Level 4 Evidence) of experts in population studies of osteoporosis (Primary and Secondary), in bone loss risk factors and in clinical trials provide a vital context to understanding the osteoporosis risk in astronauts.

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XI. ACRONYMS AND ABBREVIATIONS

BAP	Bone-specific alkaline phosphatase
aBMD	Areal bone mineral density
vBMD	Volumetric bone mineral density
DXA	Dual-energy x-ray absorptiometry
FE	Finite Element
FEM	Finite Element Model(s)
FEA	Finite Element analysis
HRP	Human Research Program
ISS	International Space Station
ISCD	International Society of Clinical Densitometry
MRI	Magnetic resonance imaging
NTX	N-telopeptide (N-terminal cross-linking telopeptide of type I collagen)
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
RCAP	Research and Clinical Advisory Panel
UV	Ultraviolet
WHO	World Health Organization

Appendix A: Review of Bone Summit Recommendations (2010)

Skeletal Health in Long-duration Astronauts: Nature, Assessment and Management Recommendations from the NASA Bone Summit[†]

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Initial Date Submitted November 6, 2012; Date Revision Submitted March 4, 2013; Date Final Disposition Set March 20, 2013

Journal of Bone and Mineral Research

DOI 10.1002/jbmr.1948

DISCLOSURES

EO has received consultancy fees, grant/research support, and/or has served on advisory boards for Amgen, Merck & Co and Eli Lilly; EO was also a member on NASA's Research on Human Health Risks, Institute of Medicine of the National Academies. RA has received consultancy fees and grant/research support from Amgen and/or Eli Lilly. SA has received consultancy fees and serves on an advisory board for Merck & Co. and has received grant/research support from NASA Human Research Program. NB has received consultancy fees and/or received grant/research support from Amgen, Merck & Co. and Eli Lilly. EML has received grant/research support, served on advisory boards and/or served on a Speakers Bureau for Amgen, Eli Lilly, Merck & Co and Novartis. SP has served on a Speakers Bureau for Amgen and is employed as a bone densitometry and endocrine consultant to NASA-Johnson Space Center. NW has received honoraria, consultancy fees and/or grant/research support from Amgen, Eli Lilly, Novartis and Merck & Co.

All other authors state that they have no conflicts of interest.

ABSTRACT

Concern about the risk of bone loss in astronauts due to prolonged exposure to microgravity prompted the National Aeronautics and Space Administration to convene a Bone Summit with a panel of experts at the Johnson Space Center to review the medical data and research evidence from astronauts who have had prolonged exposure to spaceflight.

Data were reviewed from 35 astronauts who had served on spaceflight missions lasting between 120 and 180 days with attention focused on astronauts who (a) were repeat fliers on long-duration missions, (b) were users of an Advanced Resistive Exercise Device, (c) were scanned by quantitative computed tomography (QCT) at the hip, (d) had hip bone strength estimated by finite element modeling, or (e) had lost > 10% of areal bone mineral density at the hip or lumbar spine as measured by dual-energy X-ray absorptiometry (DXA). Because of the limitations of DXA in describing the effects of spaceflight on bone strength, the panel recommended that the U.S. space program use QCT and finite element modeling to further study the unique effects of spaceflight (and recovery) on bone health in order to better inform clinical decisions.

Keywords: spaceflight, osteoporosis, QCT, Finite Element Modeling, DXA, fracture, microgravity

INTRODUCTION

Since the early days of manned spaceflight, the U.S. National Aeronautics and Space Administration (NASA) has been concerned about potential adverse effects of prolonged weightlessness, including bone atrophy due to the lack of forces (muscular and gravitational) on the skeleton (1-4) and general deconditioning under spaceflight conditions (2, 5-8). Consequently, the major thrust of research has focused on better understanding the pathophysiology of increased urinary excretion of calcium (9, 10) and loss of areal bone mineral density (aBMD) at weight-bearing skeletal sites (11). With the construction of the International Space Station (ISS), these concerns reached a higher level of importance, since astronauts were now capable of living and working in space for extended durations and potentially suffering adverse skeletal consequences. The risk of fractures is of particular concern upon re-exposure to mechanical loading, such as during the exploration of unknown planetary terrain or return to Earth's full gravity field. Moreover, cumulative skeletal deconditioning could increase the risks for premature osteoporosis and for fractures in later life.

Limited data exist for understanding the bone loss and fracture risk in astronauts. Typically, NASA astronauts are young to middle-aged (ranging from 25 to 55 years), and are predominantly male (male: female ratio ~ 5:1). In contrast to patient populations with recognized risk factors for bone loss and fracture, astronauts are physically fit and healthy. Despite this, it is plausible that long-duration spaceflight (defined by NASA as longer than 30 days) would have measurable detrimental short and long-term impacts on bone health. Typically, long-duration astronauts have lived aboard a spacecraft, such as Mir or the current ISS, for 120-180 days and the skeletal effects of these missions are not easily modeled on Earth. Equivalent to a rare syndrome, space-induced bone loss is expected to affect only a small number of individuals, the

total of which will probably not exceed 100 by the end of the ISS program in 2020. Table 1 outlines specific characteristics of the long-duration astronaut cohort as of 2010.

The complexities of spaceflight-induced bone loss in a small understudied population raise the question of whether current assessments of skeletal health in astronauts are sufficient. NASA is legally and ethically responsible for providing a safe and healthy work environment (12). Bone strength must be considered in the selection of candidates for the corps of astronauts that will participate in future flights. In addition, skeletal deficits due to spaceflight that persist after return to Earth's gravity should be monitored as they might predispose astronauts to premature fragility fractures soon after return to Earth or later in life.

It is a current medical requirement to assess the skeletal integrity of all astronaut candidates by dual-energy X-ray absorptiometry (DXA), and to monitor bone health of all active and retired NASA astronauts likewise by triennial measurements of bone density. Moreover, DXA scans are required before and after missions in all ISS astronauts, i.e., those with prolonged habitation of space (>30 days), to evaluate the skeletal effects of spaceflight and to monitor the restoration to preflight status. However, many other tests for evaluating the skeletal effects of spaceflight, including assays for gonadal hormones and quantitative computed tomography (QCT), are by astronaut consent only. Regardless of the technique used, it is difficult to investigate the effects of space on bone, or of the different interventions for bone loss in the flight environment, when the number of long-duration astronauts is so small.

To solicit clinical guidance, experts in osteoporosis, endocrinology, rheumatology, gerontology, and physical medicine and rehabilitation, with subspecialties in bone densitometry, bone epidemiology, male osteoporosis, and nutrition, were convened by NASA in 2010 as a Bone Summit Panel. The Panel was to evaluate what NASA is currently doing to manage an occupational risk for fractures that may occur later in life. The panel was asked to recommend the

skeletal measures that would be useful for the selection of astronauts and the surveillance of premature osteoporosis, the measured outcome that would serve as a trigger for possible medical intervention, and the measures that should be used to evaluate the efficacy of countermeasures being studied during spaceflight. As noted, evaluating trends in astronaut data is limited by the measures available, the delayed accumulation of data and the small sample size of astronauts. The Bone Summit Panel reviewed all available bone-relevant data accumulated from long-duration astronauts who served on the Mir spacecraft and/or the ISS. All data were from astronauts who are employed by NASA; no biomedical data from cosmonauts or astronauts employed by the international space agencies were released for chart review. Tools for risk surveillance and recommendations for future research developed at this conference are presented here.

CHARGE TO BONE SUMMIT PANEL

The panel was asked to review data relevant to mineral metabolism and to bone structure, density, turnover and strength that were collected from long-duration astronauts from 1994 to 2010. Over this period, data were acquired from 35 long-duration astronauts. All measures conducted immediately postflight were within one month of landing. These data included (a) the effects of resistive exercise during flight on aBMD (g/cm^2) as measured immediately postflight by DXA, (b) levels of endocrine regulators and biochemical markers of bone remodeling, (c) changes immediately postflight in DXA measures, (d) changes immediately postflight in compartmental volumetric BMD (vBMD, mg/cm^3) of cortical and trabecular bone as assessed by QCT, and (e) serial changes in both DXA and QCT measurements after return to Earth.

During a closed session, medical records of individual long-duration astronauts were reviewed. The 25 cases were selected (with some duplication) due to the presence of a unique trait or an extreme skeletal response to space, as follows: (a) female (n=6), (b) repeat fliers on long-

duration mission (n=4), (c) users of new (since 2009) advanced resistive exercise device (ARED) for the weightless environment (n=5) , (d) those scanned by QCT (n=10), (e) those with hip bone strength estimated by finite element modeling (FEM)—a computational tool used to estimate failure loads of complex structures (n=7) , and (f) those with a loss of aBMD > 10% in either the hip or spine (n=6). In addition, relevant published data studying long-duration astronauts were reviewed. Some preliminarydata from research studies currently in progress had been available for review but are not included here. This report summarizes the data presented and the Panel's conclusions and recommendations.

LONG-DURATION ASTRONAUT DATA: BONE LOSS AND RECOVERY

Densitometry and Biochemistry

DXA. Since 1998, NASA medically required measurements of aBMD by DXA to assess skeletal integrity of astronauts. NASA's medical standards for bone health in astronauts include T-score cut-points (NASA-STD-3001 NASA Space Flight Human System Standard, Crew Health); a T-score of -1.0 or less at the hip or lumbar spine has disqualified an applicant from the astronaut corps, partially because of the expectation that an astronaut might develop at T-score of -2.0 or less after spaceflight, based on a calculated average monthly loss of 1.0-1.5% aBMD during long-duration spaceflight (11). Among astronauts selected, this criterion also serves as a reason for disqualification from long-duration missions. When considering the use of any countermeasure to prevent bone loss, it is expected that the intervention will ensure that an astronaut returns from a mission with a T-score of -2.0 or better.

Figure 1 displays astronaut medical data that were available at the time of the Bone Summit, which includes the first 23 ISS expeditions. Changes in aBMD due to spaceflight have been quantified by serial DXA whole-body measures or regional scanning of the hip (total hip,

femoral neck and trochanter), lumbar spine, and forearm (Figure 2). Notably, after spaceflight all long-duration astronauts showed a loss in aBMD exceeding the least significant change (LSC) in at least one of these skeletal regions (4), and some astronauts had a >10% aBMD loss at both the hip and lumbar spine.[1] However, no long-duration astronaut returned from spaceflight with a hip or lumbar spine T-score less than -2.5. The panel was asked how NASA should interpret and utilize these data to assess fracture risk in astronauts.

According to NASA medical health standards (12), the preflight aBMD requirement for flight certification is based on an estimated total spaceflight-related decline in aBMD originally reported in 18 cosmonauts (11). An average monthly rate of aBMD loss was calculated from data from Mir missions (conducted from 1995 to 1998) ranging in duration from 4 to 14 months (11) and was used to predict likely aBMD loss for other mission designs. Although there were insufficient measurements to assess whether the loss during flight was linear, there was an overall average 1.0-1.5% aBMD decline per month for hip and lumbar spine. This finding highlighted the accelerated rate of aBMD loss at weight-bearing skeletal sites during spaceflight, contrasting starkly with the typical age-related rate of bone loss of 0.5% to 1.0% per year for comparable sites in older individuals on Earth. A similar rate of flight-related bone loss was found in U.S. crewmembers on ISS expeditions flown from 2000 to 2009. Since 2009, the availability of the Advanced Resistive Exercise Device (ARED) on the ISS (Figure 3A) may have attenuated the aBMD decline in the astronauts (14) by providing load-bearing exercise up to 600 pound force (lbf). This exercise capability contrasts with that of the previously-used Interim Resistive Exercise Device (iRED) (Figure 3B), which provided only one-half of the resistance loading of the ARED.

[1] Hologic QDR 4500 and QDR 2000 were used for measurement of astronaut BMD. For QDR 4500, LSC is 0.019 (trochanter), 0.035 (femoral neck) and 0.025 g/cm^2 (lumbar spine) and the LSC for the Hologic QDR 2000 was 0.024 (trochanter), 0.050 (femoral neck) and 0.035 (lumbar spine) g/cm^2.

Coincident with the change from using iRED to ARED, the averaged monthly loss in aBMD decreased from roughly 1.0% (n=24 iRED users) to 0.3-0.5% per month (n=11 ARED users to-date, unpublished data not shown). Likewise, there is a consistent trend, observed in data from 45 different long-duration crewmembers (15), for aBMD to increase in the postflight period (Figure 4). However, there is considerable heterogeneity in the extent to which aBMD is regained after flight with some astronauts appearing to have a persistent deficit. Notably, DXA measurement of aBMD is often the only index considered when evaluating the efficacy of in-flight bone loss countermeasures and the return of bone health following flight. Overall, there is concern that DXA may underestimate skeletal risks due to spaceflight and re-ambulation on Earth, highlighting the potential utility of expanding measurements of bone beyond DXA aBMD to obtain enhanced estimations of bone strength and fracture risk (16).

Quantitative Computed Tomography. In 1998, a flight experiment was conducted to evaluate the effects of spaceflight on QCT parameters at the hip and lumbar spine in ISS astronauts (17, 18). Whole bone geometry and vBMD of cortical, trabecular, and integral bone (cortical + trabecular) were measured 30-60 days before spaceflight, 7-10 days after landing, and 1 year after landing (17, 18). In ISS astronauts (n= 16), vBMD declined at variable rates (Table 2A) at lumbar spine and hip trabecular and integral bone measurement sites (17). Spaceflight resulted in a reduction in total hip bone mineral content. As reported, the reduced volume of cortical tissue (cm^3), in combination with a stable total tissue volume (cm^3) suggested that cortical thickness was reduced because of endocortical resorption (17). In the spine, accelerated vBMD losses that occurred in integral bone were comparable to losses in trabecular bone (17). QCT measures of the lumbar spine did not provide additional information about spaceflight-induced changes above and beyond DXA aBMD (17). In contrast, as further described in Table 2B, QCT can provide additional information at the hip regarding spaceflight-induced changes, and recovery

after return. QCT revealed that after 12 months of re-ambulation on Earth, total hip bone volume increased at both the proximal femur (total hip) and femoral neck whereas the vBMD was still decreased (ratio Postflight vBMD /Preflight vBMD <1, Table 2B) (18). This re-adaptation to Earth's 1-G field in middle-aged astronauts is reminiscent of the expansion of bone's cross-sectional area observed with aging in terrestrial populations and with weight loss (19, 20). Therefore, as part of a study extension, a fourth QCT hip scan was obtained 2-4 years after flight in 8 of the original 16 ISS crewmembers. Figure 5 displays different patterns of recovery in the hip and spine as assessed by DXA and QCT scans. In Figure 5A, there is a tendency for aBMD to recover in the lumbar spine (L1-L4) after return while trabecular vBMD, in QCT scans of L1 and L2 (Figure 5B), declines after the first year in all but one astronaut. A similar discordant pattern is noted in 5C and 5D where femoral neck aBMD in most individuals increased over the first year after return to Earth; however, in one astronaut whose femoral neck aBMD exceeded preflight measurements four years after return, showed a reduction in trabecular vBMD over the same period (21).

Finite Element Modeling. To translate bone density data to an estimation of bone strength, finite element models (FEM) were developed from hip QCT scans of 11 ISS astronauts (17, 22). FEM is a computational tool that estimates hip strength (in Newtons, N, of force) for specific loading orientations (Table 3). FEM detected a significant decline in hip strength after spaceflight (group means ± standard deviation [SD]) for two modeled orientations of loading (axial loading in one-legged stance and posterolateral loading that assumes falling backward to the side) (22). When declines in hip strength were divided by total months in space, as similarly reported for loss of DXA aBMD, the monthly decrease in FEM estimates of hip strength are approximately double the monthly rate of decrease in aBMD (Table 3) (22). Figure 6 shows the correlation between the spaceflight-related (preflight to postflight) changes in FEM strength and

aBMD. There was little correlation between DXA and either of the two loading models (R^2= 0.23 for one-legged stance and R^2=0.05 for posterolateral fall) (22). These data do not indicate whether DXA or FEM is superior in predicting bone health but do suggest that FEM may capture changes in bone that DXA does not (22).

Bone Turnover Markers. Figure 7 displays the group trends in biochemical markers of bone turnover from U.S. crewmembers aboard both the ISS and Russian Mir spacecraft (23). The data for N-telopeptide (NTX) measures from 24-h non-fasted urine specimens suggest that bone resorption increased early during long-duration missions and remained elevated throughout the period of weightlessness but was restored to baseline status upon return to Earth (23). In contrast, the concentration of bone-specific alkaline phosphatase (BAP), a marker of bone formation (Figure 7), was reduced or unchanged during spaceflight (23), suggesting that an uncoupling of bone resorption and formation occurs. The increase in bone resorption, without an increase in bone formation, could be expected to yield net loss of bone mass.

In-flight Countermeasure Evaluations

Resistive exercise is the only countermeasure routinely used to mitigate bone loss in all long-duration astronauts. The ARED (Figure 3A) was flown to the ISS in December 2008 to supplement the iRED (Figure 3B), along with the cycle ergometer and treadmill exercise hardware that have also been used in flight since 2000. In the few ARED users in which data have been obtained (Figure 2), the average monthly loss in aBMD (n=8) was reduced to 0.47±0.53% (group mean ±SD) at the total hip with an average monthly gain 0.30±0.94% at the lumbar spine – compared with monthly losses of 1.1 $\pm$0.45 (total hip) and 0.71 $\pm$0.51 (lumbar spine) in aBMD with use of the iRED (n=24). As described below, the interpretation of this apparent change is confounded by the use of bisphosphonates in three of the astronauts during the period of ARED availability.

Pharmacologic measures could also be considered to counter flight-related bone loss. To this end, bisphosphonate therapy during spaceflight is being studied in a joint experiment by NASA and the Japan Aerospace Exploration Agency (JAXA). The study is testing bisphosphonates (alendronate or zoledronic acid) to prevent loss of bone mass, structure, and strength at the hip, quantified by DXA, QCT and FEM, in long-duration astronauts. The study was approved for testing in astronauts, with a planned statistical comparison to 16 historical controls (17, 18). However, only alendronate has been offered to U.S. astronauts because of NASA's concern about the limited safety data for zoledronic acid relative to alendronate. Participants in the bisphosphonate flight study also had access to ARED for resistive exercise, whereas the historical controls did not. Thus, the attenuated postflight aBMD loss detected in ARED users will be confounded by the anti-resorptive effects of alendronate in the exercising astronauts. The data from this bisphosphonate trial are not available for presentation here as the study is ongoing.

BONE SUMMIT PANEL RECOMMENDATIONS

Overall Assessment

Long-duration astronauts can experience 10- 20% aBMD decline during a spaceflight mission and still meet NASA standards for bone health. In the panel's opinion, interventions to mitigate bone loss during spaceflight are advisable for long-duration astronauts, in order to minimize risk for adverse skeletal effects later in life. However, because the long-term adaptation of bone to space has only been evaluated in a small number of astronauts, the panel considers the available data insufficient to confidently recommend a specific therapeutic course of action. Additional well-designed studies are warranted.

Measures of bone structure (such as trabecular microarchitecture, whole bone geometry, 3-dimensional mass distributions in cortical and trabecular compartments) are key

determinants of bone strength (24) that could be uniquely affected by weightlessness and may not be sufficiently accounted for by DXA technology. The available data (reviewed above) suggest QCT-based measures may provide distinct information about bone health in astronauts. The specifics of these changes and how they influence the fracture risk of an astronaut with re-loading are not well understood. Moreover, if spaceflight-induced changes persist, then they could combine with later age-related changes and prematurely increase fracture risk later in life. Thus, the impact of space-induced skeletal changes on hip strength will remain an open issue for NASA until structural indices of bone in long-duration astronauts, such as those acquired with QCT, can be serially evaluated.

A resolution of the relative merits of aBMD vs. QCT measures in this situation is hampered by novel constraints, including understudied exposure variables (spaceflight), small numbers of affected individuals, variation in subject characteristics (age, training, flight duration and conditions). Nevertheless, the potential value of additional measures should not be ignored. Hence, the panel recommends that all long-duration astronauts be evaluated for spaceflight-induced changes in separate compartments of the hip (total, femoral neck, and trochanter) by conducting preflight and postflight QCT-based measures. Also, the Panel recommends that QCT measures be incorporated in a surveillance program and the evaluation of astronaut eligibility and that efforts to better understand the appropriate role of QCT measures should be ongoing. The heterogeneous changes in the spine with aging, however, are problematic and a surveillance regimen for the spine cannot be recommended at this time beyond monitoring BMD and vertebral fracture assessments with DXA. However, new technologies and analyses should be explored in research studies to generate data for the panel's review in the near future.

Based upon its review of trends in astronaut data and individual case reports, the Bone Summit Panel offered the following recommendations for bone health management in long-duration astronauts: (a) expand the characterization of spaceflight changes to include QCT of the hip for risk surveillance, (b) investigate the impact of spaceflight on hip bone strength with the use of FEM, and (c) modify current risk mitigation approaches before, during and after spaceflight to optimize effectiveness.

QCT for Risk Surveillance

The sole reliance on DXA to assess spaceflight effects and countermeasure efficacy may provide inadequate information to NASA decision-makers. Although aBMD as measured by DXA may be a robust predictor for osteoporosis-related fractures in the general population, it may be insufficient for understanding fracture risk in astronauts. First, the astronaut population is physically fit but exposed to novel environmental conditions and mission activities in microgravity that may have unique effects on bone. Standard aBMD-based clinical guidelines for monitoring fracture risk and assessing therapeutic efficacy are derived from terrestrial populations who are generally older and with conventional clinical risk factors (e.g., menopause, rheumatoid arthritis, glucocorticoid treatment, falls, etc.).

Second, aBMD measures may not adequately detect the unique changes induced by spaceflight and postflight reloading. DXA, for example, cannot distinguish cortical restructuring (i.e., modeling) that has occurred as the result of spaceflight, that could occur with exercise loading of bones during spaceflight, or could occur after return to Earth's gravity (18). An increase in cortical bone will likely overwhelm the aBMD measure and mask quantitatively less impressive but biomechanically important effects in trabecular bone. Although not fully understood, other indices of bone structure (such as trabecular microarchitecture, whole bone geometry and cross-sectional dimensions, and cortical bone width) are recognized determinants of

bone strength, but are poorly measured with DXA (24, 25). The available astronaut data suggest that spaceflight may result in a unique form of bone loss with structural implications not adequately assessed by aBMD measures. Data from both QCT and DXA indicate that skeletal changes caused by spaceflight are specific to skeletal regions and to bone compartments (4, 11, 30). Moreover, there is a precipitous rate of aBMD decline in crewmembers (4, 11), that may be due in part to the aggressive osteoclast activity inferred from iliac crest biopsies of skeletally-unloaded bed rest subjects (26-28). Bone turnover markers suggest uncoupled bone remodeling during spaceflight (23), a condition that could result in the formation of stress risers in trabecular bone (32). Similarly accelerated losses in postmenopausal women can result in microarchitectural disruptions and increased fractures, especially at central skeletal sites (31). The failure of hip trabecular vBMD to return to preflight values by 2 years after return is of concern (21), especially since deficits in trabecular vBMD of the femoral neck were reported to predict hip fracture independent of aBMD in elderly men (25). Thus, the space-induced changes in bone quality could put an astronaut at a higher fracture risk than the average Earth-based person with the same aBMD. The persistent structural deficits after spaceflight also could be further worsened by changes induced by a second flight as well as by aging or other risk factors (21, 29).

Although the exact contribution of trabecular bone loss or structural change on hip strength requires further definition, the absence of recovery-to-baseline measurements in trabecular bone indicates irreversible changes in strength have probably occurred. Therefore, it could be clinically meaningful to implement QCT hip scans to assess the efficacy of new in-flight countermeasures and for surveillance postflight, where an absence of recovery could be a trigger to review bone health risk factors and/or to consider intervention to prevent expected age-related bone loss. The specific changes to bone microarchitecture (e.g., trabecular thickness, trabecular

separation, connectivity, etc) and their impact on strength and fracture risk will require further research since QCT does not detect trabecular microarchitectural changes.

It is recognized that a recommendation based on an established relationship between QCT-based measures and fracture risk is a standard that is impossible to meet considering the limited data available on astronauts. Nevertheless, the uncertainties associated with the assessment of bone character with aBMD in astronauts suggest that more sensitive and innovative approaches may be required for longer-term surveillance. It is recommended that measurement of bone structure and of separate bone compartments using QCT should be instituted. With the end of the Space Shuttle program, launches and landings of crew transport systems would occur in Russia; thus, the panel recommended that QCT measures be conducted in the U.S. as close as possible to launch and landing dates.

Finite Element Modeling for Estimations of Hip Bone Strength

The collective evidence from spaceflights raises the possibility that prolonged space habitation affects the skeleton in such a way that declines in mechanical strength may not be detected by current clinical technologies (17, 21, 22). Computation of QCT-FEM strength can complement the existing medical assessment tests (DXA and bone turnover markers) and the more conventional QCT structural indices. As mentioned above, declines in bone strength, estimated by FEM, are evident after spaceflight, in spite of the pristine medical history and extreme physical fitness of the typical astronaut before spaceflight (22). Emerging data indicate that FEM estimates of hip strength may be related to fracture risk (33-35), especially in combination with aBMD. FEM estimates of hip failure load quantify the ability of the hip to resist fracture for a specific load vector. This index may be the single best existing composite assessment of bone strength because of its ability to integrate applied loads with geometry and distribution of material properties (BMD, elastic modulus, and yield strength) in 3-D bone

structure (36). While there are no data to indicate that FEM estimation of strength is an improved index compared to aBMD, the use of multiple determinants of bone strength (36) by FEM, in conjunction with the single aBMD surrogate for bone strength, may enhance the assessment of fracture probability in each astronaut for individualized clinical decisions. Finally, data from QCT and FEM strength modeling can be used to optimize a probabilistic fracture model, developed by NASA, to calculate applied loads to bones and fracture probability (37). This, and other modeling efforts, could be used for estimating fracture risk during exploration missions on planets or asteroids, monitoring risk during return to normal activities on Earth, and for understanding the combined effects of two long-duration missions or of spaceflight changes with the expected age-related changes. As surveillance data accumulate for the astronaut population, recommendations for future extended missions beyond low Earth orbit should be formulated or modified.

The possibility of low-trauma postflight fractures is a critical driver for assessment and appropriate intervention. The combination of space effects with postflight aging may predispose long-duration astronauts to fragility fractures at an earlier age on Earth. FEM has been applied to QCT scans from aging population cohorts, in which FEM-estimated hip strength is associated with incident hip fractures (33, 34). Such modeling could also be used to direct bone rehabilitation efforts after astronauts return to Earth, to avoid the risk of overloading bones, especially with exercise. The translation of QCT data to FEM strength provides an individualized functional index at the hip for each astronaut. From the occupational risk perspective, bone medical standards based on QCT data and FEM estimation of hip fracture loads could provide NASA with the clinical practice guidelines needed for advising astronauts against physical activities with high impact loads to the hip. These data may provide the basis for developing new medical standards to supplement the current aBMD-based standards. This translation -- from measured surrogates for bone strength to calculated estimates of bone strength – could add

confidence when addressing important issues: are an individual astronaut's hip bones strong enough to perform mechanically-loaded tasks on a mission; to return to preflight activities on Earth; to accommodate age-related bone loss?

Given the constraints of low subject numbers and slow data acquisition, attempts should be made to use the most powerful research technologies and analyses available to identify astronauts who may be at risk for developing premature osteoporosis. Thus, it is recommended that NASA evaluate hip strength with QCT-derived FEM estimates as a new surrogate to assess fracture risk following long-duration spaceflight. Additional results are accumulating from ongoing terrestrial studies, which will help to inform the interpretation of astronaut data.

Risk Mitigation Approaches

Preflight Selection and Certification Standards

- The NASA Space Flight Human System Standards (13) are criteria to establish ranges of crew health required to optimize health and performance during spaceflight missions. Consequently, these medical standards -- for selecting applicants for astronaut candidacy, for certifying an astronaut for a spaceflight mission or for disqualifying an astronaut from a second spaceflight mission – could be used to protect those astronauts who are at greater risk for losing bone strength during spaceflight that would put them at increased fracture risk with subsequent aging. The current standards are based upon aBMD by DXA, which may not capture all parameters of bone strength and fracture risk. Therefore, NASA should expand the use of QCT-based FEM estimates of hip strength as a selection standard for bone health. The growing literature that links FEM measures of strength to fracture probability provides a basis for the practical application of these measures in astronauts.

In-Flight Countermeasures

- NASA cannot validate any single in-flight mitigation strategy as long as multiple bone-loss countermeasures are applied in individual astronauts.

- There is limited information about side effects of pharmaceutical agents under weightless conditions. Thus, NASA should continue to focus on management strategies of modifiable risk factors for bone loss (by exercise and dietary manipulations) as the standard methods for bone loss prevention during ISS missions before using Earth-based pharmaceutical interventions. This recommendation may be refined in the future as accumulated data, and research on emerging pharmaceuticals, are reviewed

- Preliminary, but limited, flight data for alendronate are encouraging and suggest that treatment may mitigate hip bone loss during flight (38). However, the onset of the alendronate study coincides with the implementation of new ARED hardware; therefore, it is not possible to distinguish the contribution of each intervention on the prevention of aBMD loss or the underlying structural changes. Studies are required to compare intervention by combined alendronate and ARED exercise with intervention by only the ARED exercise.

- If an on-orbit pharmaceutical intervention is deemed necessary for longer missions, then the panel suggested zoledronic acid be considered for the in-flight experiment based on two major considerations: (a) a single intravenous (IV) infusion of zoledronic acid may be preferred to weekly oral alendronate, or other oral bisphosphonates available, because of the association of oral bisphosphonates with adverse upper gastrointestinal effects and the knowledge gaps related to esophageal adhesiveness and pill dissolution in the microgravity environment, and (b) the preflight administration of an IV bisphosphonate would enable flight surgeons to address any side effects while astronauts are still on Earth.

- Denosumab may be useful, but long-term clinical data are only now emerging and are needed to identify possible low-frequency adverse events.
- Teriparatide might be effective for crewmembers who do not regain BMD with conventional treatments over an extended postflight period.
- All agents being considered for flight may require appropriate testing, including in ground-based spaceflight analogs, before undertaking trials in astronauts.
- There is some concern for in-flight stress fractures and fractures that may occur during in-flight exercise on the new ARED exercise hardware.
- QCT testing should be part of the evaluation of the efficacy of all in-flight countermeasures to mitigate or prevent losses in hip trabecular vBMD.
- Because the impact of changes to the trabecular microstructure of the hip is not known and may be irreversible (39), NASA should help continue to develop technologies that can be used to understand changes in trabecular microarchitecture at sites in the hip and spine of astronauts.

Postflight Surveillance

- Continued use of DXA for risk surveillance is recommended for astronauts because of the abundance of aBMD data from terrestrial populations as reference cohorts for aging effects.
- Decisions regarding spaceflight-induced skeletal loss, for both clinical care and subsequent flight certifications, should not rely solely on measures performed using DXA. As QCT measures become available on individual astronauts, they should be incorporated into the postflight clinical evaluation of skeletal status.

An osteoporosis specialist should evaluate astronauts for treatable risk factors if his/her DXA postflight aBMD T-score is < -2.0 or if hip QCT results do not recover to preflight values (within Least Significant Change of preflight measure) by two years after return. Although flight-induced loss of vertebral strength should not be ignored in future studies (for instance with QCT), the astronauts are now of an age at which some osteophytic change is conceivable, and, since extra-vertebral mineralization may obscure aBMD change in the spine, the primary measurement site should be the hip. Vertebral fracture assessment (VFA) is a recent addition to medically required DXA scans and should continue to be conducted in all astronauts during DXA tests.

SUMMARY OF RECOMMENDATIONS

1. Given the few numbers affected and the unique nature of the problem, the adverse effects of spaceflight on the skeleton can be considered a form of rare syndrome. In light of the current understanding of its pathophysiology and the preliminary data available, the adoption of novel assessment methods (e.g. QCT, FEM) is appropriate.

Although useful, the current aBMD-based fracture standards for risk assessment (originally developed in older women) are probably not sufficient for assessing risk in astronauts. Pre- and postflight QCT hip scans should be collected on astronauts to evaluate the impact of spaceflight on structural determinants of bone strength. FEM estimates of hip strength, as performed in terrestrial population studies, should be analyzed to derive hip strength cutoffs as new medical standards for bone health in astronauts, e.g., to qualify astronauts for long-duration spaceflight and to evaluate applicants for the astronaut corps.

2. As QCT-based assessments of bone health are refined, the current use of aBMD measures for pre- and postflight assessments should continue. DXA generates minimal cumulative radiation exposure and enables simultaneous monitoring of changes in body composition. Moreover, DXA monitoring will add to the available, historical dataset on

astronauts and additional aBMD data collected in parallel with new QCT measures will considerably add to the understanding of bone change associated with spaceflight, the development of appropriate countermeasures, and the assessment of postflight bone health.

3. For ISS missions, NASA should focus on reducing known modifiable risk factors for bone loss, such as reduced physical activity and sub-optimal nutrition.

4. The use of pharmacological interventions is of interest to reduce spaceflight-associated bone loss. The design of future studies on the utility of such interventions should be carefully considered to ensure clear outcomes.

ACKNOWLEDGMENTS

Appreciation is extended to Dr. Angelo A. Licata (Cleveland Clinic, Center for Space Medicine) and Dr. S.V. Reddy (Medical University of South Carolina) for their thoughtful review of this manuscript and to Dr. Jane Krauhs and Dr. Kathleen McMonigal, M.D. (both of Johnson Space Center) for their editorial assistance. In addition, authors wish to acknowledge the contributions of Dr. Scott M. Smith, Dr. Sara R. Zwart, Dr. Andrea M. Hanson, Dr. Harlan Evans, Ms. Elisabeth R. Spector, and Ms. Adriana Ba biak-Vazquez (all of Johnson Space Center), Dr. Adrian D. LeBlanc (Universities Space Research Association), Dr. Thomas F. Lang (University of California at San Francisco), and Dr. Joyce H. Keyak (University of Ca lifornia at Irvine) for the presentations of astronaut data in this review. The Bone Sum mit activity was funded by Human Adaptation and Countermeasures Division at NASA Johnson Space Center.

Authors' Roles: JS convened the Bone Sum mit Panel, developed the charge to the panel, drafted the manuscript and was responsible for th e integrity of the data presented herein. EO provided extensive manuscript revision. EO and SA provided guidance to JS on the relevant astronaut data to review and f acilitated discussion sessions at the Bone Sum mit. The Bone Summit Panel (EO, RA, SA, NB, ML, SP, SS, MS , and NW) provided the interpretation of the astronaut data, formulated the recommendations, revised the manuscript content and approved the final version of the manuscript.

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FIGURE LEGENDS

Figure 1. Areal BMD T-scores for Skeletal Regions of Hip and Spine in Astronauts before and after ISS Missions. T-scores were calculated according to procedures of the International Society for Clinical Densitometry (ISCD) from pre- and postflight measurements of areal BMD by dual-energy x-ray absorptiometry (DXA). Thirty sets of preflight to postflight measurements were from 27 different US astronauts (23 ISS spaceflight expeditions, some with multiple or previously flown US crewmembers). Changes in T-scores are superimposed on the ISCD diagnostic guidelines for osteoporosis (T-scores < -2.5) developed for perimenopausal and postmenopausal women, and men over the age of 50. T-scores between -1.0 and -2.5 represent the low bone mass range (osteopenia). These diagnostic criteria were the only evidence-based guidelines available for evaluating skeletal integrity when BMD measurements by DXA became the medically-required test for long-duration astronaut crew health (NASA Med Vol. B). Clinical decisions and medical standards for human health and performance at NASA are based upon these diagnostic guidelines.

Figure 2. Distribution of DXA Areal BMD Percentage Changes after Long-duration Mir or ISS Spaceflight. Percentage change of preflight areal BMD (aBMD) *per month* was calculated by subtracting the first postflight DXA BMD measurement from the preflight measurement and normalizing by the mission duration (typically 4-6 months). Data are plotted for groups of crewmembers who served on Mir (n= 28 cosmonauts and 7 U.S. astronauts), on ISS with access to only the interim Resistive Exercise Device [iRED] for weight-bearing exercises (n=24 U.S. astronauts), and on ISS after the Advanced Resistive Exercise Device [ARED] became available (n=8 crewmembers). BMD changes are reported for lumbar spine (LSpine), femoral neck (Fem.Neck), trochanter, total hip, and wrist. (Wrist is 1/3 radius+ ulna, and is for

ISS crewmembers only.) All mean aBMD changes from preflight to postflight, for all groups, were significant ($p < 0.05$), as determined by Student's *t* test (one-tailed, paired), except for the effect of ARED on lumbar spine and wrist ($p<0.06$ for trochanter). ARED users include crewmembers who were concurrently taking a bisphosphonate (n=3), crewmembers with access to ARED for < 4 months (n=3), in addition to crewmembers with ARED access for the entire spaceflight (~6 months) and not taking bisphosphonates (n=2). Astronaut measurements had to be combined to ensure non-identifiable data.

Figure 3A. Advanced Resistive Exercise Device (ARED). A crewmember performs a deadlift exercise on the ARED, which delivers up to 600 pound force (lbf) resistance exercise. Installed in December 2009, the ARED is used by crewmembers 3-6 days per week. It can provide high loads to the lower back, hip, knee, and ankle joints. The group mean declines in aBMD during flight appear reduced since the ARED was made available on the ISS, although in some of these astronauts, the beneficial effects of ARED on aBMD may be in combination with bisphosphonate use. In two cases, postflight aBMD has increased for lumbar spine relative to preflight BMD. Photo courtesy of NASA.

Figure 3B. Interim Resistive Exercise Device (iRED). A crewmember performs a squat exercise on iRED. The iRED hardware was the primary mode of resistance exercise on the ISS from mid-2001 to 2010. The iRED delivered up to 300 lbf of resistive force through two canister assemblies (~150 lb each). BMD losses were reported at ~1.1% per month when the iRED and treadmill only were available for crew use. Photo courtesy of NASA.

Figure 4. Representative Trends in Areal BMD Recovery in the Lumbar Spine (A) and Femoral Neck (B) after a Long-Duration Mission. The percentage change in areal BMD (aBMD) from the preflight value is plotted as a function of days after landing (when DXA scans were performed). The scatterplot displays both longitudinal and cross-sectional data from U.S.

and Russian long-duration crewmembers (n=45) from 56 different long-duration missions ("pluses" denote data from a repeat flier). Data were fitted to a mathematical equation (solid line) with 95% confidence limits (dashed lines). The intersection of the horizontal dotted line with the y-axis = 50% of the average bone loss due to spaceflight and the intersection of the vertical dotted line with the x-axis = the number of days needed to recover 50% of lost bone ("Half Life"). In general, the recovery of aBMD for all sites measured was prolonged, with the time needed to regain mass being greater than the time for loss of mass to occur. Recovery of aBMD does not necessarily reflect a recovery pattern for bone strength. (Adapted from 15)

Figure 5. Different Individual Trends in QCT and DXA Data of the Lumbar Spine and Femoral Neck of ISS Astronauts after Return to Earth. Eight crewmembers of the original sixteen who participated in the QCT flight study (17) consented to an additional scan to evaluate recovery beyond one year after return to Earth. The fourth QCT scans were performed between two and four years after landing because of the staggered dates of return. The postflight volumetric BMD (vBMD) and areal BMD (aBMD) measurements were normalized to the preflight BMD (the y-axis) and plotted as a function of days after landing (the x-axis) when the scans were performed. In Figure 5A, the postflight DXA measurement of aBMD of the lumbar spine (L1-L4) increased in all eight astronauts and continued to increase or stabilize over the next 2-4 years while, in Figure 5B, the QCT measurement of vBMD in the trabecular compartment of the lumbar spine (L1 and L2) increased in two of eight astronauts during the first year of re-ambulation on Earth. After the first year, trabecular vBMD declined or stabilized (some at a level below baseline measurement) in six of eight astronauts. For the femoral neck, in Figure 5C the DXA measurement of aBMD for two astronauts exceeded or returned to the preflight measurement during the postflight monitoring period while, in one of these same astronauts, the QCT measurement of vBMD in the trabecular compartment Figure 5D) declined over the same

time period (Reprinted from Acta Astronautica, Vol 67, RD Carpenter, Long-Term Changes in the Density and Structure of the Human Hip and Spine after Long-Duration Spaceflight, pp 71-81, Copyright 2010, with permission from Elsevier"(21)).

Figure 6. Spaceflight-induced Changes of Hip Bone Strength in ISS astronauts. Hip bone strength of ISS astronauts before and after spaceflight was assessed by preflight and postflight scans of hips by both DXA and QCT. FE models of QCT data estimated hip bone strength for two loading scenarios (single-legged stance and posterolateral fall) whereas hip areal BMD (aBMD) represents the *widely-applied surrogate* for bone strength. The y-axis is the change in hip strength estimated by FEM and the x-axis is change in aBMD as a DXA-measured surrogate for hip bone strength. There was poor correlation (Stance: R^2=0.23; Fall:R^2=0.05) between these two methods for assessing changes, suggesting that QCT and FEM detect changes in hip bone strength due to spaceflight that are not captured by DXA aBMD (Adapted from 22).

Figure 7. Bone Remodeling during Spaceflight Assessed by Biomarkers of Bone Turnover. Changes in bone turnover biomarkers, measured in urine and blood obtained before, during, and after spaceflight, are used to reflect cumulative changes in bone cell activities. N-telopeptide (NTX) (n=11) in urine (% change from preflight measure) and bone-specific alkaline phosphatase (BSAP, U/L) (n=6) produced in circulation by osteoblasts were measured in crewmembers on the Mir spacecraft and the ISS. Biomarkers highlight the uncoupling of bone remodeling during spaceflight. Bone resorption was elevated early and persisted throughout spaceflight, whereas bone formation was unresponsive to the stimulation of bone resorption, resulting in net bone loss. FD#: Number of flight days into the mission, R+#: Number of days after return to Earth. The vertical lines denote the temporal separation of in-flight from postflight samples (Adapted from 23).

Table 1. Characteristics of the Long-Duration Astronaut Cohort (29 men and 6 women) at time of Bone Summit (2010).

Data by Flight	**Astronauts on Long Duration Missions**	
Mean+SD	Males	Females
Typical space mission duration (days)	161 ± 36 (58-215)	165 ± 39 (90-194)
Average age at time of flight (years)	47 ± 5 (37-55)	45 ± 4 (90=194)
Body mass index (BMI)	25.8 ± 2.0 (21.2 to 30.7)	23.4 ± 2.4 (20.4 to 25.9)
Body weight (kg)	80 ± 6 (63 to 97)	67 ± 8 (57 to 82)
Height (cm)	176 ± 6 (163 to 185)	170 ± 4 (165 to 178)
Total body lean mass (kg)	61 ± 5 (45 to 69)	47 ± 5 (39 to 54)
Total body fat mass (kg)	16 ± 4 (6 to 27)	19 ± 7 (13 to 33)
% Body fat	Males 20 ± 4 (9 to 27)	Females 27 ± 8 (19 to 41)

In 2010, relative to the NASA Astronaut Corps (total 331 astronauts), the cohort of long-duration astronauts is 33 astronauts and predominantly male (ratio of males to females 29:6 or 4.8:1). Of this group 4 astronauts have served on two separate long-duration spaceflights out of a total of 39 separate spaceflight missions. All values in table are means + SD (with range in parentheses). The traits of the corps have been consistent with time; over the two years since the Bone Summit, the total number of long-duration crewmembers has increased to 55, the number of repeat fliers has increased by 1 and the total number of flights has increased by 12. *For computed averages, the

astronaut data (e.g., age, duration, body composition data) for the 2nd flight was treated as if another separate astronaut.

Table 2A Changes in the Hip (Femoral Neck and Trochanter) and Lumbar Spine Measured in Astronauts after Return from Missions on the International Space Station (ISS). .

Index DXA aBMD	**% /Month n=14**	**Index QCT vBMD**	**% Change /Month n=14**
Lumbar Spine	-0.8 ± 0.5	Integral Lumbar Spine	-0.9 ± 0.5
		Trabecular Lumbar Spine	-0.7 ± 0.6
Femoral Neck	-1.1 ± 0.5	Integral Femoral Neck	-1.2 ± 0.7
		Trabecular Femoral Neck	-2.7 ± 1.9
Trochanter	-1.2 ± 0.9	Integral Trochanter	-1.5 ± 0.9
		Trabecular Trochanter	-2.2 ± 0.9

All values are means ± SD of areal Bone Mineral Density (aBMD) by Dual -Energy X-ray Absorptiometry (DXA) and of volumetric BMD (vBMD) by Quantitative Computed Tomography (QCT) performed in identical ISS astronauts (n=14). Integral vBMD is measurement of combined cortical and trabecular bone (17). At the lumbar spine, QCT measurement of vBMD did not generate additional information beyond DXA aBMD. Measurements were conducted as soon after spaceflight as possible (i.e., within 21 days) (17).

Table 2B. Changes at the Hip (Femoral Neck and Proximal Femur) with Re-ambulation on Earth by QCT Measurements in 16 ISS Astronauts

	% Spaceflight Change Mean± SD	% Re-ambulation Change Mean ±SD	Ratio Postflight 1 yr/Preflight
FEMORAL NECK			
Total vBMD (g/cm^3)	-9.4 ±6.4*	0.9± 5.9	0.91**
Total BMC (g)	-10.8± 10.6*	8.1 ± 11.8*	0.96
Cortical Volume (cm^3)	-8.0 ± 11.2*	8.0± 11.8*	0.99
Total Volume (cm^3)	-1.4± 10.9	7.2±9.9*	1.05
TOTAL PROXIMAL FEMUR			
Total vBMD (g/cm^3)	-10.4 ± -9.7*	4.4±4.7*	0.93**
Total BMC (g)	-11.1 ±11.2*	12.2±11.8*	0.99
Cortical Volume (cm^3)	-9.2±10.8*	11.5±12.2*	1.01
Total Volume (cm^3)	-0.7 ±10.1*	7.2±7.3*	1.06

All values in table for volumetric bone mineral density (vBMD), bone mineral content (BMC), cortical and total bone volumes are group means ± SD for ISS astronauts (n= 16). Data for two additional crewmembers were obtained since the earlier report in 2004 (17). Absolute BMD values were used to generate the ratio of postflight to preflight measurements. *Significant ($p<0.05$) difference from preflight values; ** significant difference between 1 year-postflight from preflight measurements (18).

Table 3. Hip Bone Strength from Finite Element Models of QCT Data from 11 Long-Duration Astronauts Before (Preflight) and Immediately After (Postflight) ISS Missions

Loading Condition	Preflight	Postflight	P value
Stance	13,200 N ± 300 N	11,200 N ± 2400 N	<0.001
	2.2% loss/month		
Fall	2,580 N ± 560 N	2,280 N ± 590 N	<0.003
	1.9% loss/month		

Hip strength (force to failure, in Newtons [N]) is estimated for two loading orientations from finite element models of QCT scans. All values are group means ±SD for ISS astronauts (n= 11). Average calculated monthly loss in hip strength was calculated from total percentage loss over mission divided by total months of spaceflight [22]. Immediate postflight QCT scans after ISS missions were performed within one-month of landing due to travel to site of preflight QCT scanner.

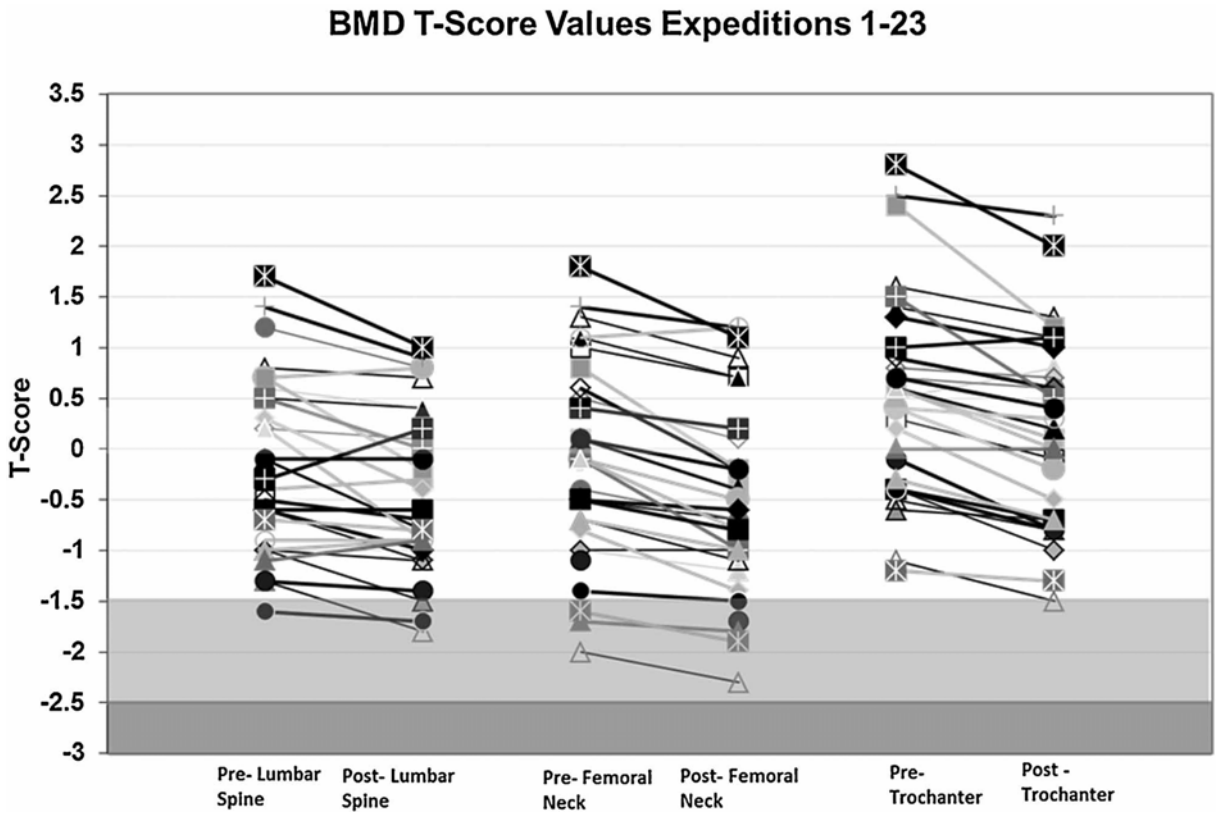


Figure 1

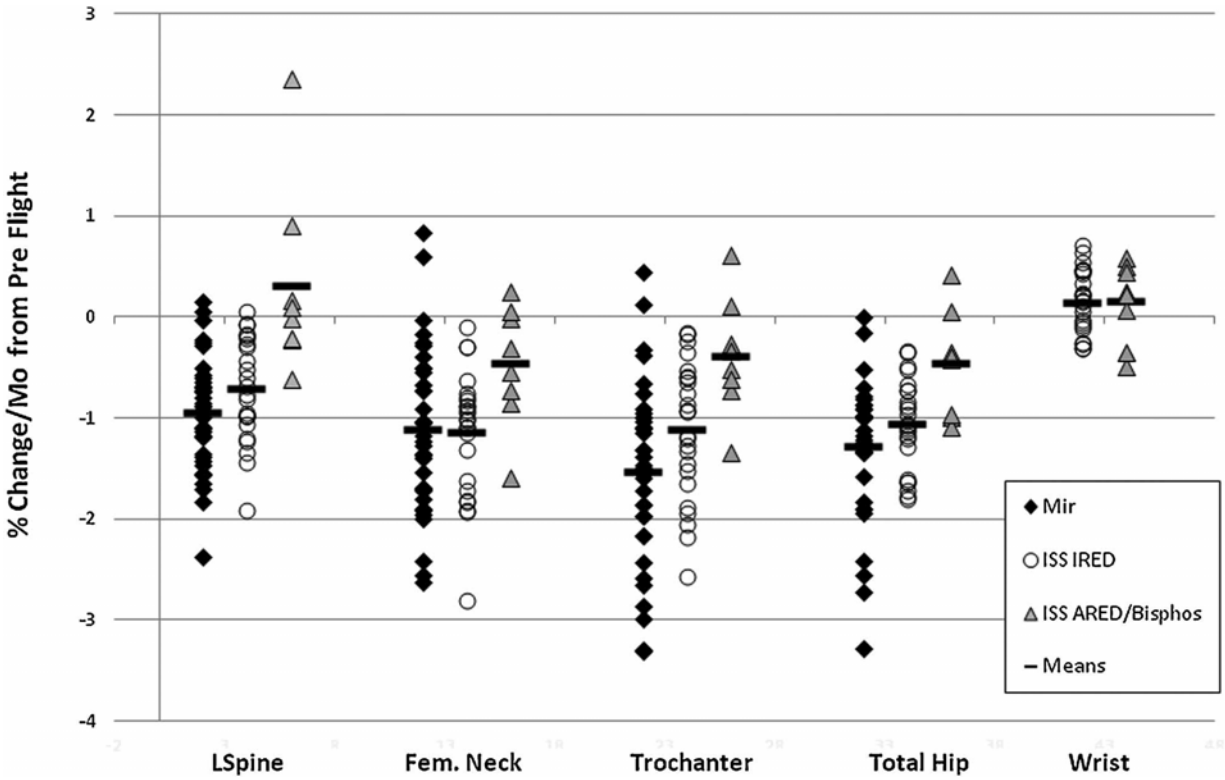


Figure 2

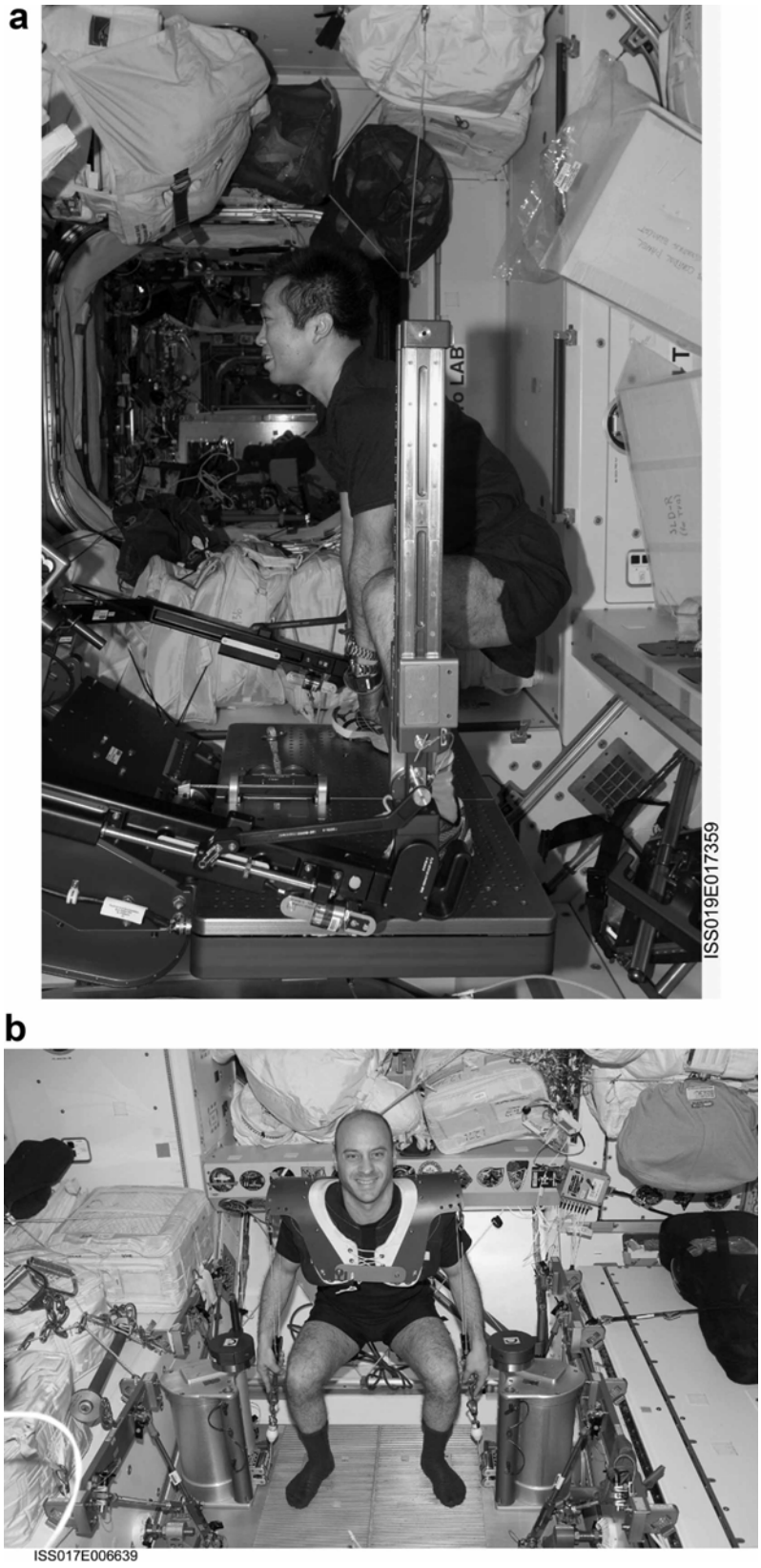


Figure 3

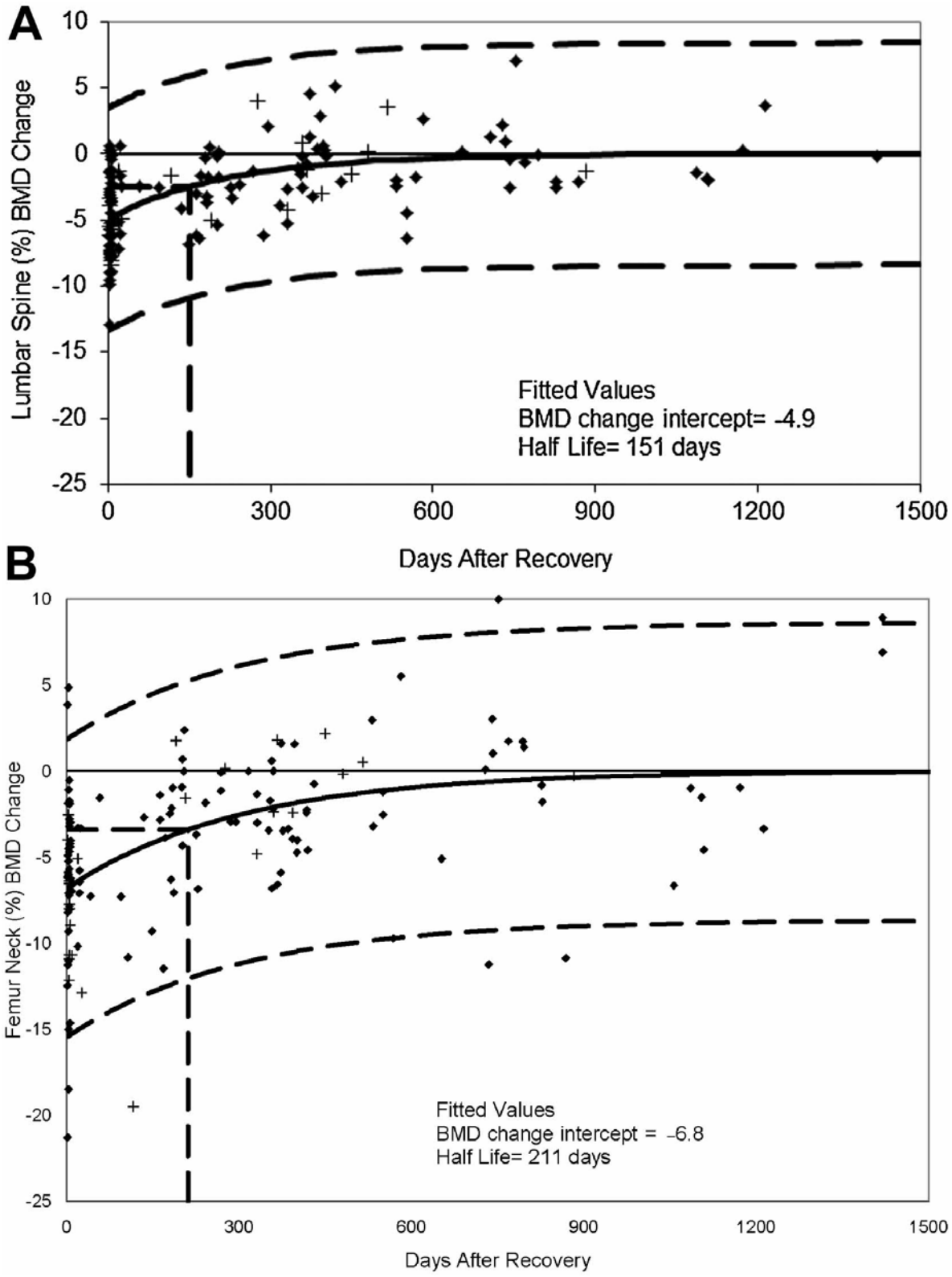
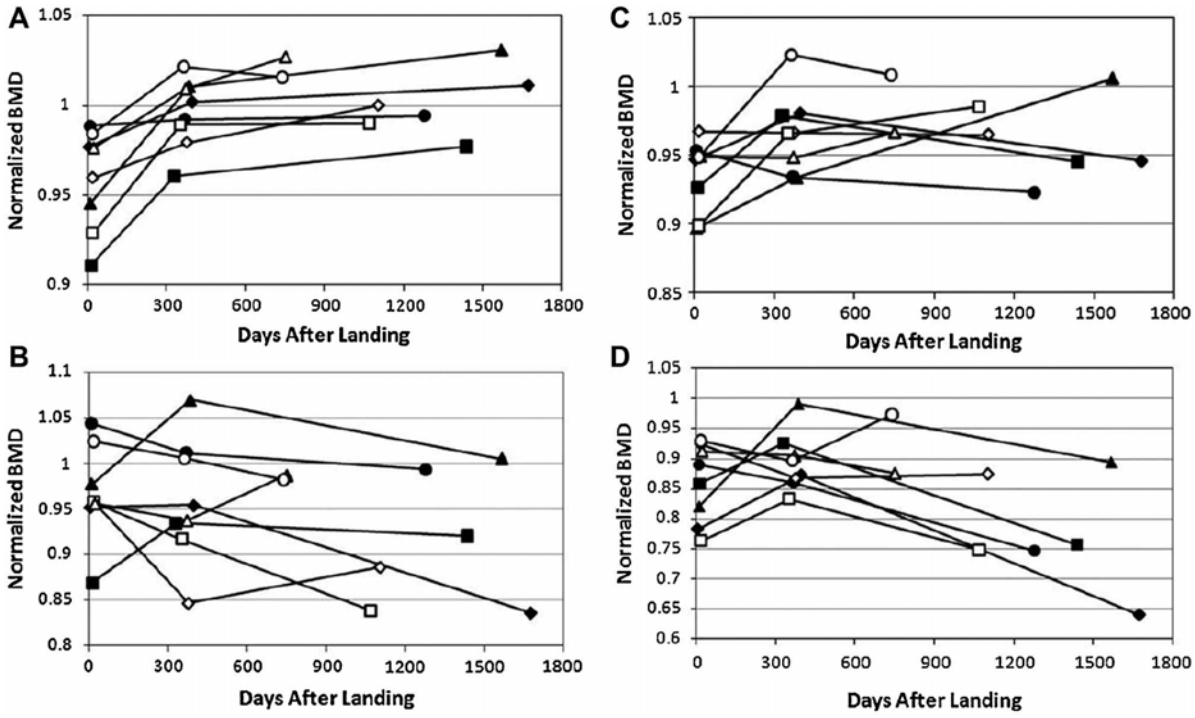


Figure 4



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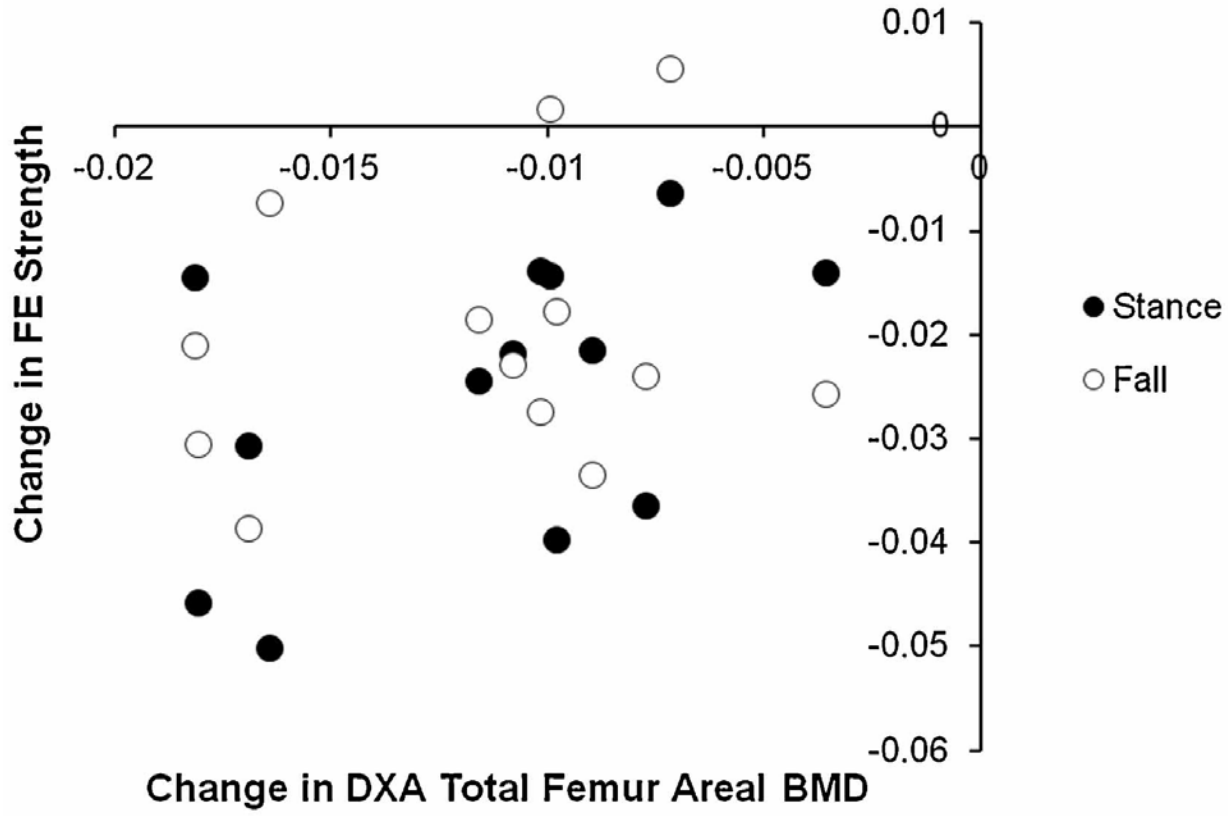

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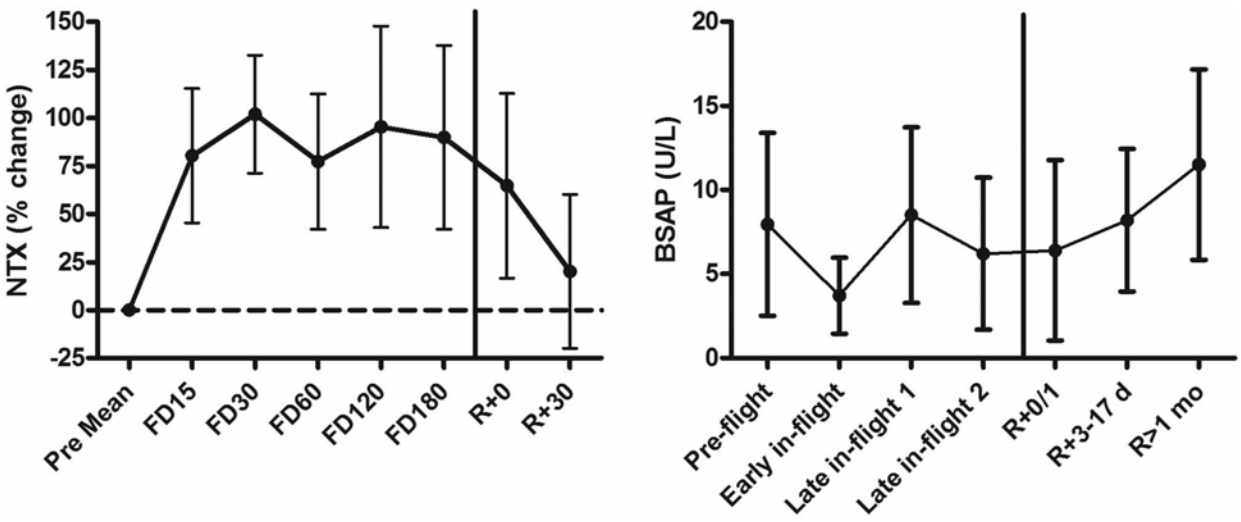

Figure 7

Appendix B. Executive Summary Bone Summit II (2013)

This Executive Summary is the recommendations and key comments expressed during discussions held at the NASA Bone Summit II in Houston, TX on November 4 and 5, 2013. The Bone Summit Research and Clinical Advisory Panel [RCAP] that was first assembled in 2010 was reconvened in Houston for the Bone Summit II in November 2013. The RCAP was charged to review bone data collected from additional ISS astronauts (n=10) since the 2010 Bone Summit (n=35). The new case reports of ISS astronauts included DXA areal BMD, QCT BMD, biochemistry, and any available information to elucidate possible risk factors (e.g., in-flight exercise activity level, specific medication intake during flight, fracture history, family history of osteoporosis, history of metabolic disorders, menopausal status for females, preflight terrestrial exercise level). As per its own recommendation, the Bone Summit RCAP evaluated data in order to refine and/or affirm its previous recommendations to use QCT for risk surveillance.

At the conclusion of Bone Summit II, the RCAP recommended reconvening at 3-year intervals to evaluate all accumulated bone relevant biomedical data to-date. Bone Summit III is planned for 2016.

Key comments and recommendations at Bone Summit II:

- Medical Assessment Test - Bone Densitometry. The RCAP reiterated that percent of areal BMD loss (DXA measurement) alone is not a predictor for bone fracture. **Recommendation**: Accumulate more data, describing changes to bone structure, to supplement DXA areal BMD measurements, especially after prolonged exposure (>30 days) to spaceflight. NASA should also research emerging technologies for assessing changes in bone microarchitecture of the hip, spine and wrist (radius), with the aim of identifying irreversible changes due to spaceflight.
- Risk Surveillance. The RCAP determined that the astronaut QCT data to-date were not sufficient at this time to support its acceptance as a medical test with specific guidelines or its elimination as a surveillance technology. **Recommendation**: QCT hip measurements should be continued as previously detailed (in 2010). The potential utility of Trabecular Bone Score [TBS] from DXA scans should be assessed. Collecting peripheral QCT data, especially for radial changes, should be considered.
- Fracture Prediction Models. The RCAP was briefed on a NASA-developed *Bone Fracture Module* for a Probabilistic Risk Assessment [PRA] of fracture during specific Design Reference Missions [DRM] (e.g., ISS, deep space asteroid, lunar habitation, Mars mission). The NASA PRA tool revealed that a risk for fracture in weightless conditions of spaceflight is greater than the RCAP perceived. **Recommendation:** This tool should be validated with terrestrial data from aging populations, and other estimates for bone strength in astronauts (aside from areal BMD) should be tested in the module. In addition, the RCAP recommended exploring the use of former applicants to astronaut candidacy as a control group for long-term fracture risk.
- Osteoporosis Therapies. The RCAP was asked about the increasing number of therapeutic agents entering the market and if any should be considered for long-duration missions. **Recommendation**: For a 3-year Mars DRM, priority should be given to a long-acting, single injection pharmaceutical agent, i.e., zoledronic acid.
- DXA Test Frequency. The RCAP was informed that active astronauts have BMDs measured by DXA on a triennial basis. The RCAP was asked if this interval should be extended. **Recommendation**: The intervals by which DXA scans are performed for risk assessments should be *individualized*, which may reduce or extend the interval. The contracted clinical consultant in bone endocrinology should order the timing of the next DXA scan.
- Biochemical Markers. The RCAP was asked if the current panel of bone turnover markers (N-telopeptide; osteocalcin and bone-specific alkaline phosphatase) could be improved. **Recommendation**: Measurement of serum CTX (collagen type 1 cross-linked C-telopeptide) for bone resorption and P1NP (type 1 pro-collagen N-terminal) for bone formation should be implemented to be consistent with standardized clinical assessment of biochemical markers for bone

turnover and archived specimens in the registry should be assayed for these markers (Vasikaran S et al. Bone Marker Standards Working Group, Osteoporos Int 22(2):391). In addition, in order to inform the clinical interpretation of flight biochemistry data, research flight data should be collected to characterize i) gonadal hormone levels and ii) the circadian rhythms of space on bone turnover markers.

- Vitamin D Dosing. The Medical Operations Group asked the RCAP to recommend a vitamin D dose for use during spaceflight. A 50,000 IU loading dose for restoring crewmembers to normal range before spaceflight is currently recommended by the contracted clinical bone endocrinologist. **Recommendation**: Once Vitamin D is in the optimal range in astronaut, a 2000 IU vitamin D dose should be given daily during spaceflight to best mimic endogenous production. **Comment to crew surgeons:** Individual variation is to be expected.
- Bisphosphonate Use. The Medical Operations Group requested a recommendation for bisphosphonates to prevent bone loss during spaceflight missions. The RCAP considers the calculated deficit in BMD during a Mars mission of 3 years an unacceptable risk factor for fracture. This conclusion was based upon i) the averaged rates of BMD decline (for hip and spine) observed in astronauts and ii) the perceived inability to fly an ARED-like exercise hardware on the smaller-sized crew exploration vehicle (Orion). **Recommendation**: The Bone Summit RCAP recommends a single Reclast (zoledronic acid) injection for astronauts flying on missions greater than 365 days due to the safety concerns of an oral dosage (a greater probability of gastric irritation and possible esophageal ulceration). An infusion before launch (e.g., one-three months) may be protective for up to three years (Grey et al.; Results from a randomized double-blind placebo-controlled trial indicate five years of anti-resorptive activity after a single dose of Zoledronate. Bone 50(2012):1389-1393). **Comment to crew surgeons**: Prodromal symptoms (fever, muscle aches for 2-3 days) may be expected, but symptoms are transient and can be addressed in the prelaunch period.
- In-flight Physical Activity Level. The RCAP noted the difficulty of interpreting an impact of in-flight exercise (i.e., resistive), and of changes to body composition, on BMD changes. **Recommendation:** Collect information (e.g., clinically-applied questionnaires) that will adequately capture the changes in levels of physical activity (between preflight, in-flight and postflight) of the astronauts.
- Treatment for Hypersensitivity: Astronauts will be exposed to rodent allergens[1] during animal experimentation performed during spaceflight. Crew surgeons questioned the RCAP about the use of glucocorticoids (medication known to induce bone loss) to reduce the symptoms of hypersensitivity in astronauts during missions. **Recommendation**: Anti-histamines should be used, if possible, to avoid the risk of glucocorticoid-induced bone loss (with > 3 month treatment). The possibility of glucocorticoid treatment supports the recommendation to pretreat crewmembers with Reclast (zoledronic acid) to mitigate expected bone loss (as performed with organ transplant patients on Earth).
- Fracture Healing in Space: Forteo is currently used to treat patients with severe osteoporosis (<-2.5 T-score) or with a fragility fracture. There is some off-label use of Forteo in sports medicine to facilitate fracture healing in athletes. In 2010, the RCAP recommended inclusion of Forteo in the inflight med kit for longer-duration missions; in-flight availability of Forteo requires temperature-controlled storage. **Recommendation**: No new recommendations.
- Nutrients and bone/kidney. **Comment:** The effects of spaceflight and of mission constraints on bone turnover and mineral metabolism need integration with the assessment of bone densitometry.

[1] Note: Astronaut exposure to mice may confound clinical immunoassays that use mouse antigens and monoclonal antibodies. Immunoassays/lab tests that employ goat antigens may be an alternative approach.

Overall, NASA's strategy of assessing relative fracture risk in astronauts by T-score BMD-based guidelines alone needs to be refined. Accurately determining the absolute fracture risk in astronauts is an ambitious goal that may never be fully realized. A concerted effort however should be made to expand NASA's technical and scientific capabilities toward objectively assessing the factors contributing to the risk since long-duration space flight is expected to: i) have profound and possibly irreversible bone changes that would not be adequately addressed by DXA BMD, ii) affect other physiological systems (e.g., muscle) that determine fracture likelihood and iii) expose astronauts to novel situations that involve a greater probability of overloading bones.

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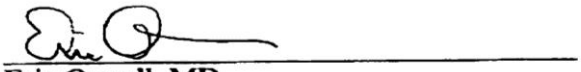

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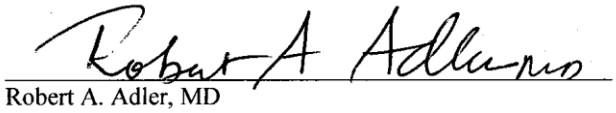

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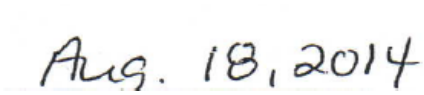

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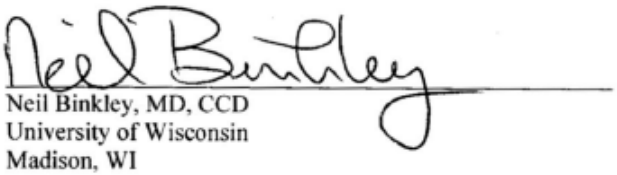

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List of Acronyms and Abreviations

ARED – Advanced Resistive Exercise Device

aBMD – areal Bone Mineral Density

BMD – Bone Mineral Density

CTX - collagen type 1 cross-linked C-telopeptide

DRM – Design Reference Mission

DXA – Dual-energy X-ray Absorptiometry

FEM – Finite Element Model or Finite Element Modeling

FRAX – Fracture Risk Assessment Tool

HRP – Human Research Program

HR-pQCT – High Resolution Peripheral Quantitative Computed Tomography

ISS – International Space Station

IU – International Units

LSAH – Lifetime Surveillance of Astronaut Health

P1NP - type 1 pro-collagen N-terminal

PRA – Probabilistic Risk Assessment

QCT – Quantitative Computed Tomography

RANKL – Receptor activator of nuclear factor kappa-B ligand

RCAP – Research and Clinical Advisory Panel

TBS – Trabecular Bone Score

USRA – Universities Space Research Association

Appendix C. Executive Summary Bone RCAP 2016

This Executive Summary documents the recommendations and key comments expressed during discussions at a meeting of the NASA Bone Research and Clinical Advisory Panel 2016 in Houston, TX, on October 24 and 25, 2016. The Bone Summit Research and Clinical Advisory Panel (RCAP) was first assembled in 2010 as a Bone Summit, reconvened in Houston for Bone Summit II in 2013, and will be chartered as a Bone RCAP following the October 2016 meeting.

The Bone RCAP 2016 was charged with reviewing biomedical and research data collected from ISS including chart reviews for astronauts who had flown since the 2013 Bone Summit. Reviewed data included areal Bone Mineral Density (aBMD) by Dual Energy X-ray Absorptiometry (DXA), compartmental volumetric BMD (vBMD) by Quantitative Computed Tomography (QCT), serum and urine biochemistry of mineral metabolism, and any available information to elucidate possible risk factors (e.g., pre- and in-flight exercise activity levels, specific medication intake during flight, fracture history, family history of osteoporosis, history of metabolic disorders, menopausal status for females, pre-flight terrestrial exercise level). As per its previous recommendation, the Bone RCAP reconvenes to evaluate data in order to refine and/or affirm its previous recommendations to use QCT for risk surveillance.

Key comments and recommendations of Bone RCAP 2016:

1. Skeletal Health Surveillance:
   The RCAP reviewed the presentation of the Bone Clinical Practice Guideline [CPG] currently in operation at Johnson Space Center. The CPG is for monitoring and maintaining skeletal health in astronauts during and after an astronaut's career and is undergirded by NASA Crewmember Medical Standards (Selection and Periodic Certification of crewmembers for spaceflight) and by the Medical Evaluation Document (MED) Volume A (medical standards for ISS crewmembers). Both sets of medical requirements for bone health are grounded on the evaluation of *abnormal* bone mineral density [BMD] i) to diagnosis osteoporosis and ii) to evaluate "osteopenia" as a trigger for further endocrine evaluation. The recent enhancements to Bone Health monitoring, approved and presented by NASA clinicians to the RCAP, are consistent with positions of the ISCD (International Society for Clinical Densitometry) and of the NOF (National Osteoporosis Foundation) which define ranges of normal bone mineral density with age and integrate FRAX-estimated 10-year fracture probabilities (both hip and major osteoporotic fracture). ***Recommendation:*** Assess vertebral bone health with TBS much earlier in the clinical-decision flow chart as per routine DXA scanning.
2. Risk Surveillance (additions to standard medically-required DXA testing):
   QCT: The RCAP reiterated that areal BMD as measured by DXA is insufficient to capture space flight-induced changes to the hip, a skeletal site predisposed to fragility fracture with advancing age. Results from the recently-completed pilot study (Hip QCT) validate the necessity for compartment-specific volumetric BMD measurements, i.e., QCT. The RCAP stressed that the knowledge gained from QCT hip measurements is critical to NASA's programmatic decision-making. ***Recommendations***: Obtain hip QCT scans on all long-duration astronauts (i.e., 6 months or longer), as per the testing schedule for the Hip QCT study, to supplement standard DXA testing. QCT testing should be coordinated with the High Resolution pQCT study (Canadian Space Agency) to acquire additional insight to space flight effects on bone microarchitecture of peripheral sites (wrist and ankle).
   Finite Element (FE) Modeling: FE modeling for estimating bone strength is not currently ready for clinical use but may add valuable information to augment QCT and DXA. ***Recommendation*:** Continue to analyze all QCT scans for Finite Element estimates of hip strength; continue research on FE-based fracture risk prediction models, including identification of FE strength thresholds as an additional index for bone health. Remain cognizant of the fact that the *rate* of bone loss, irrespective of absolute BMD or FE strength, may be of particular concern.
   Trabecular Bone Score (TBS): Trabecular Bone Score (TBS) of the lumbar spine may be a useful adjunct to standard DXA BMD, as TBS texture analysis captures elements of bone quality and is a BMD-independent contributor to fracture risk. As a consequence, the Astronaut Occupational Health Management Group at JSC has accepted TBS acquisition as part of routine surveillance of astronaut skeletal health. ***Recommendation***: Conduct TBS analysis of existing and future lumbar spine scans to investigate how space flight might influence this surrogate of bone microarchitecture and thus contribute to increased long-term fracture risk.
3. Countermeasures for Space Flight Bone Loss:
   Bisphosphonates: The RCAP agreed that the evidence for the anti-resorptive effects of alendronate to prevent disuse-induced bone loss is compelling (e.g., Bisphosphonate SMO, alendronate bed rest study). The RCAP noted large trabecular BMD losses in some ISS crewmembers including those exercising on ARED. The high *rate* of bone loss, irrespective of absolute BMD, is also of clinical concern as rapid loss is associated with increased fracture risk in postmenopausal women. Prevention of bone loss with an anti-resorptive bisphosphonate for all astronauts is warranted since a) it cannot be predicted who will lose bone quickly; b) ARED use may not be possible (equipment malfunction, crew injury, etc.); and c) the reduction of urinary calcium (Ca) excretion would contribute to the mitigation of renal stone risk. ***Recommendations:*** Provide Zoledronic acid (ZA) as a 5 mg infusion to all astronauts flying on missions of 6 months or longer. One infusion prior to flight provides logistical convenience, likely protection for missions lasting up to 3 (possibly even 5) years, and a safety profile that avoids the risk of

gastric reflux with oral preparations. For premenopausal women, discuss childbearing plans and convey the risks of bisphosphonates vs. no treatment. Treat with ZA between L-6mo and L-3mo to preclude interference of transient infusion reactions with prelaunch activities. Monitor effects of ZA treatment with DXA, QCT and biochemical markers. Continue to monitor bone density parameters in all astronauts to determine the effectiveness of ZA, and to identify characteristics of those astronauts who may lose significant amounts of bone (and thus may benefit from ZA) during shorter missions.

Exercise: Based on DXA, QCT and FE data collected to date, the RCAP agreed that ARED use appears to reduce post-flight BMD deficits (on average, by about half compared to pre-ARED). However, not all ARED users follow this trend. The RCAP reviewed NASA's Small Exercise Concepts being considered for use on missions to Mars, including assessment of several proposed devices for musculoskeletal protection (e.g., ROCKY, DART, ATLAS). This group also recognized the potential utility of integrating QCT measurements with Small Exercise Concepts testing. QCT testing would enable an assessment of proposed exercise devices on compartmental bone (e.g., loss of trabecular vBMD or gain in cortical bone volume).

Recommendations: Continue to acquire musculoskeletal data for ISS missions using ARED, as well as for testing of small exercise concept devices. Determine how exercise frequency, loading, magnitude, and motivation could relate to bone loss and recovery, and collect force plate measurements if possible. Investigate how concurrent use of ZA might allow resistive exercise loads to be reduced while still protecting other body systems and providing more accommodation for individual crew exercise preferences or needs. Review relevant data from Exercise Investigator Workshops and Working Groups.

Potential use of other pharmaceuticals: Agents other than bisphosphonates have been studied for terrestrial bone loss; these include denosumab, teriparatide and abaloparatide. None has been studied for efficacy in preventing space-flight induced bone resorption. Teriparatide and abaloparatide increase both formation and resorption on earth, and would therefore create concerns for hypercalcemia and hypercalciuria during flight. Oral contraceptives and progesterone IUDs (e.g., Mirena) are acceptable drugs for suppressing menstruation and maintaining adequate estrogen for bone; however, oral contraceptives have a higher risk of blood clots.

4. Vitamin D Supplementation:

   Vitamin D data were presented, showing the results throughout the history of ISS, as measured through research studies by the Nutritional Biochemistry Laboratory. ***Recommendations:*** Continue 25(OH) Vitamin D supplementation for all crewmembers, increasing from current dose of 800 IU/day to 1000 IU/day, with pills packaged with in-flight meals to help assure compliance. This dosing recommendation refines the dosage recommended in 2013. Start Vitamin D supplementation 3-4 months before launch, to determine whether appropriate levels have been reached before flight. Standardize Vitamin D assays (see below for more detail).

5. Biochemical Markers:

   The RCAP agreed that the clinical utility of biochemical markers for bone loss is currently unclear, but that biochemical assays remain important research tools for insight into the pathophysiology of space flight bone loss and the responses to bone-related countermeasures. The RCAP also reviewed the proposed use of stable Ca isotopes for estimating calcium balance -- this new methodology has potential for real-time monitoring of whole body bone calcium balance in flight if a device could be sufficiently miniaturized and automated. ***Recommendations:*** As recommended by the RCAP in 2013, the collection of serum and urine samples pre- in- and post-flight (e.g., via Biochemical Profile research study) should continue, along with the archiving of samples for future testing. Wherever possible, collection times and assay methods should be standardized to assure compatibility of results from different studies/time periods, and there should be a shift away from immune-based assays toward mass-spectrometry-based assays to improve specificity and reproducibility (Vitamin D, sex steroids, adrenal steroids). Information is needed regarding whether there is diurnal variability in bone remodeling/markers in space, as well as the role of the sympathetic nervous system on space flight bone loss. Continue investigation of stable Ca isotopes; the operational application of this method is promising but requires further validation and development to establish its clinical utility and affordability.

6. Evaluating Muscle Protection and Body Composition Changes: The Small Exercise Concepts (SEC) group and the RCAP as a whole discussed muscle preservation with space flight, and body composition testing. The RCAP agreed that QCT testing could also provide important information on muscle and fat in the key region of the upper thigh, beyond the soft tissue data provided by DXA. ***Recommendations***: Continue to collect QCT data before and after long-duration flights. If possible, reanalyze existing hip QCT scans for cross-sectional analysis of thigh sub-cutaneous fat and inter- and intra-muscular fat. Toward this same end, amend the current QCT protocol to add one additional scan slice of the upper thigh, with negligible increase in radiation exposure. Reanalyze all previous whole body DXA scans with recently available, software for visceral adipose tissue (VAT). Total body MRI might also be considered to assess adipose deposits and regional skeletal muscle. For lean and fat measurements, use ISCD reporting guidelines; do not employ currently-proposed cut points used for sarcopenia diagnosis. Muscle preservation overall doesn't appear to be a significant problem, but there may be a need to address small muscle groups, postural muscles, and joints and discs (the latter of which might be protected by the ability to reduce exercise loads for crewmembers on ZA). Other recommendations to consider: measure CPK (creatinine phosphokinase) to detect overuse of muscle, possibly for symptomatic muscle soreness; encourage use of activity monitors for astronauts with poor exercise compliance; monitor dietary protein intake and possibly nitrogen output. Review relevant data from Exercise Investigator Workshops and Working Groups.

The overarching aim of the Bone Summit/RCAP is to increase NASA's understanding of spaceflight effects on the skeletal health of long-duration astronauts. In 2010, the RCAP recommended use of hip QCT scans to provide risk surveillance beyond the capabilities of standard DXA measurements, specifically i) to evaluate postflight bone loss and recovery in different bone compartments of the hip; ii) to assess changes in hip bone structure; and iii) to facilitate a biomechanical assessment of hip fracture probability using Finite Element Analysis. The concluding opinion of the Bone RCAP 2016 is that QCT hip scans i) are a vital adjunct to DXA for both short-term and long-term risk surveillance of crew skeletal health and ii) provide data critical to programmatic planning of exploration class missions. Furthermore, the Bone RCAP recognizes that the adaptive skeletal response to microgravity is predominated by osteoclast-driven bone resorption that may cause irreversible changes in bone microarchitecture. Hence, the Bone RCAP recommends a pre-flight infusion of the anti-resorptive bisphosphonate zoledronic acid (ZA) as the first-line countermeasure to prevent spaceflight bone loss in astronauts embarking on missions of 6 months or longer. The Bone RCAP believes that based on current evidence these two recommendations (continued use of QCT scans to augment DXA, as well as use of ZA as a bone loss countermeasure) will maximize NASA's ability to protect the skeletal health of long-duration crewmembers in low earth orbit and beyond.

SIGNATURE PAGES

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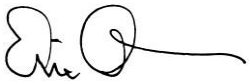

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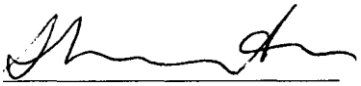

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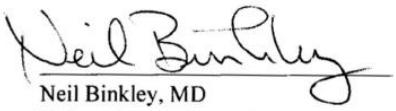

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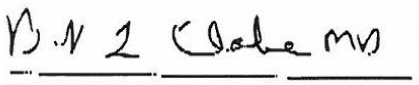

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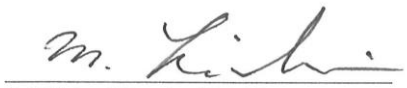

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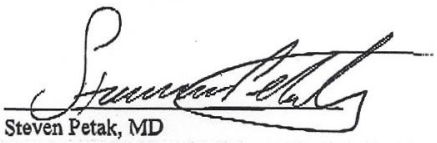

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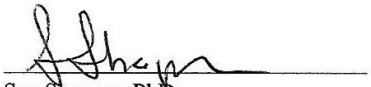

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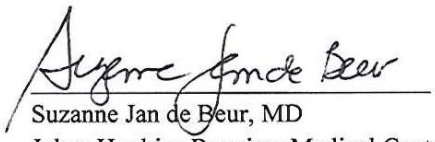

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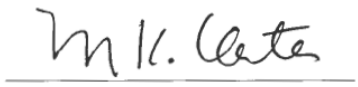

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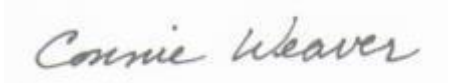

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ACRONYMS AND ABBREVIATIONS

aBMD - areal Bone Mineral Density

BMD – Bone Mineral Density

CTX – Collagen type 1 cross-linked C-telopeptide

DRM – Design Reference Mission

DXA – Dual-energy X-ray Absorptiometry

FEM – Finite Element Model or Finite Element Modeling

FRAX – a fracture risk assessment tool

HRP – Human Research Program

HR-pQCT – High Resolution Peripheral Quantitative Computed Tomography

ISS – International Space Station

IU – International Units

LSAH – Lifetime Surveillance of Astronaut Health

P1NP –Type 1 pro-collagen N-terminal

PRA – Probabilistic Risk Assessment

QCT – Quantitative Computed Tomography

RCAP- Research and Clinical Advisory Panel

TBS – Trabecular Bone Score

VAT – Visceral Adipose Tissue

vBMD – volumetric Bone Mineral Density

EXERCISE RELATED ACRONYMS

ARED - Advanced Resistive Exercise Device

ATLAS - Advanced Twin Lifting and Aerobic System

DART - Device for Aerobic and Resistance Training

MPCV - Single Cable Motorized Device

NGRED - Next Generation Resistive Exercise Device

ROCKY - Resistive Overload Combined with Kinetic Yo-Yo devise